nature OUTLOOK

Produced with support from:

newventurefund unicef GAVI ALLIANCE

A global battle to prevent disease

nature OUTLOOK

VACCINES

6 March 2014 / VOL 507 / Issue No 7490

Cover art: Nik Spencer

Vaccines are a triumph of medicine. But the project to erect immunological shields against all deadly pathogens is far from complete, as is evident in this Outlook. Despite intense research into three of the world's biggest killers — TB, malaria, and HIV — we still do not have an effective vaccine for any (page S4). Another disease that the western world has largely forgotten — polio — remains a scourge in a few poor countries. But the endgame is nigh; a strategy based on tweaking the vaccine's composition over time is on target to eradicate this paralytic disease (S14). And a form of bacterial meningitis might soon be eradicated thanks to a powerful combination: government and industry (S16).

For those diseases we can prevent, delivering vaccines to the people who need them most is far from simple. Most vaccines need to be kept within a narrow range of temperatures, lest they go bad. Progress is also being made on the ability to deliver vaccines through harsh environments without spoilage (S8).

Vaccine development, historically a hit-and-miss process, could be on the cusp of a revolution in rational design, thanks to systems biology and its holistic view of living systems (S10). A major new player has entered the vaccine market. China, trying to shake off a reputation for scandal and inferior quality, has received World Health Organization approval to produce vaccines for Japanese encephalitis (S12). Meanwhile, a growing subset of the population is opting out of vaccinations. The predictable result: outbreaks of disease in areas corresponding to the vaccine refusal movement (S17).

We are pleased to acknowledge the financial support of the New Venture Fund, United Nations Children's Fund (UNICEF), and GAVI Alliance, as well as additional support from the Bill & Melinda Gates Foundation, in producing this Outlook. As always, *Nature* retains sole responsibility for all editorial content

Herb Brody
Supplements Editor

CONTENTS

COLLECTION

Nature Outlooks are sponsored supplements that aim to stimulate interest and debate around a subject of interest to the sponsor, while satisfying the editorial values of *Nature* and our readers' expectations. The boundaries of sponsor involvement are clearly delineated in the Nature Outlook Editorial guidelines available at http://www.nature.com/advertising/resources/pdf/outlook_guidelines.pdf

CITING THE OUTLOOK
Cite as a supplement to *Nature*, for example, *Nature* **Vol XXX**, No. XXXX Suppl, Sxx–Sxx (2014). To cite previously published articles from the collection, please use the original citation, which can be found at the start of each article.

VISIT THE OUTLOOK ONLINE
The *Nature Outlook Vaccines* supplement can be found at http://www.nature.com/nature/outlook/vaccines/

All featured articles will be freely available for 6 months.

SUBSCRIPTIONS AND CUSTOMER SERVICES
For UK/Europe (excluding Japan):Nature Publishing Group, Subscriptions, Brunel Road, Basingstoke, Hants, RG21 6XS, UK. Tel: +44 (0) 1256 329242. Subscriptions and customer services for Americas – including Canada, Latin America and the Caribbean: Nature Publishing Group, 75 Varick St, 9th floor, New York, NY 10013-1917, USA. Tel: +1 866 363 7860 (US/Canada) or +1 212 726 9223 (outside US/Canada). Japan/China/Korea:Nature Publishing Group — Asia-Pacific, Chiyoda Building 5-6th Floor, 2-37 Ichigaya Tamachi, Shinjuku-ku, Tokyo, 162-0843, Japan. Tel: +81 3 3267 8751.

CUSTOMER SERVICES
Feedback@nature.com

THE AGE OF VACCINES

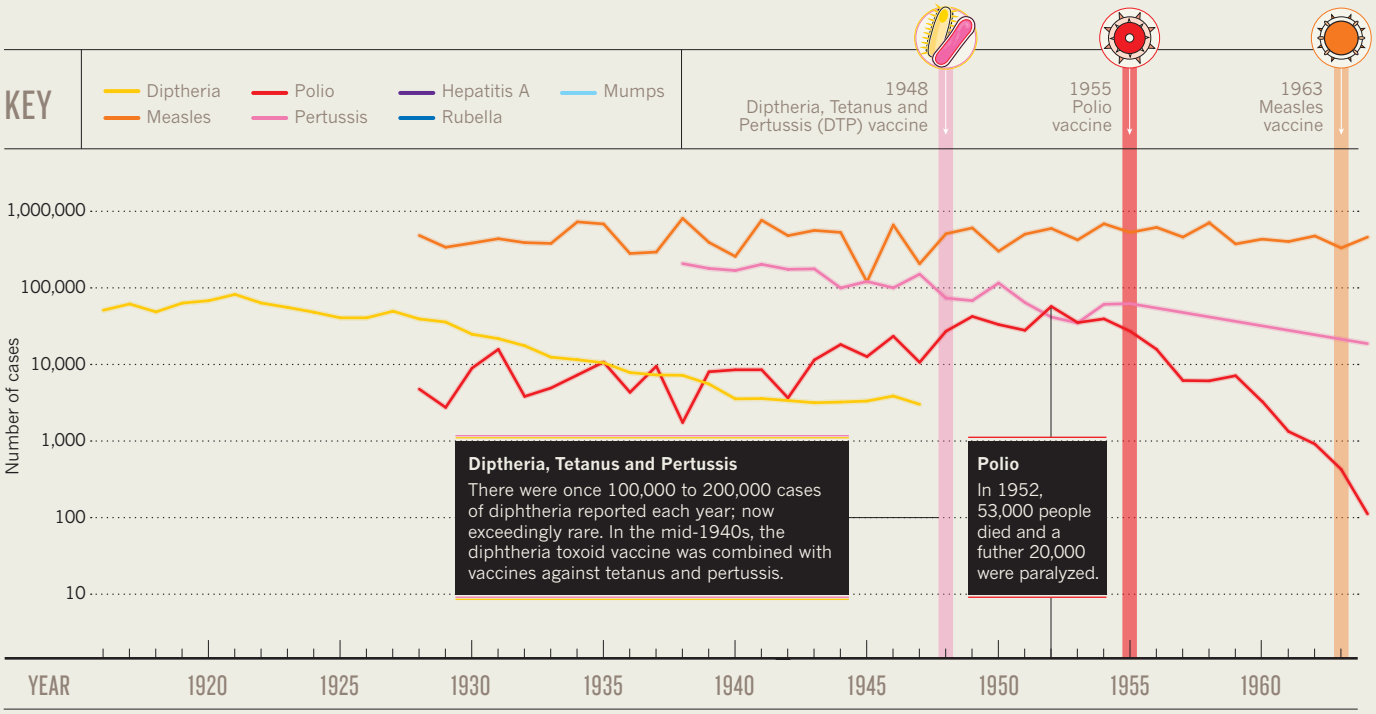
The advent of routine childhood vaccination has led to dramatic declines in many contagious diseases in the United States. Maintaining these gains there and spreading these success worldwide is challenge for public health. By **Tony Scully**.

103M

103 million cases of childhood diseases have been prevented in the United States since 1924.

A HISTORY OF DISEASE REDUCTION

An analysis of weekly disease surveillance recorded at the state level by the US Centre for Disease Control and Prevention reveals how many major threats to public health have been affected by the introduction of a vaccine; an estimated 103 million cases of childhood diseases since 1924.



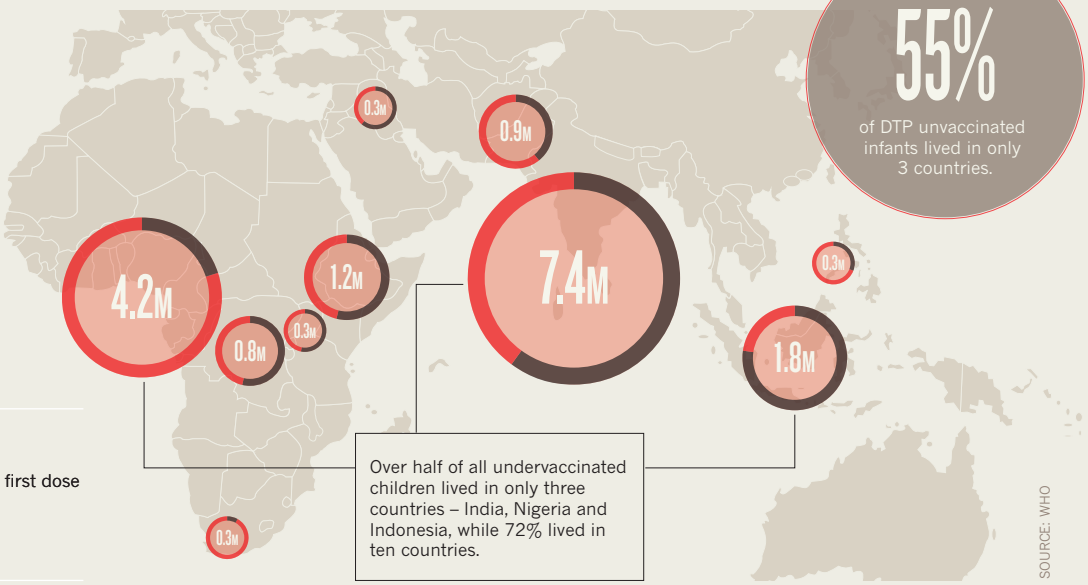
OUT OF COVERAGE

If a child receives the three doses of the DTP vaccines they are likely to have completed routine childhood vaccination – a useful proxy for routine vaccination coverage.

Among the 22.6 million children who did not receive the three doses, nearly 8.4 million started but failed to complete — pointing to poor health infrastructure. For the 14 million that never received the first dose, it seems that parental refusal is a major factor.

55%

of DTP unvaccinated infants lived in only 3 countries.



THE USUAL SUSPECTS

Several highly infectious diseases have been brought under control by routine childhood vaccination, although complacency can lead to resurgence in disease.

Diptheria
This bacterial infection can damage heart muscle and the nervous system, leading to paralysis and respiratory failure.

Pertussis
Better known as whooping cough, infection can last up to 6 weeks. Each year, 50 million cases worldwide and 300,000 deaths.

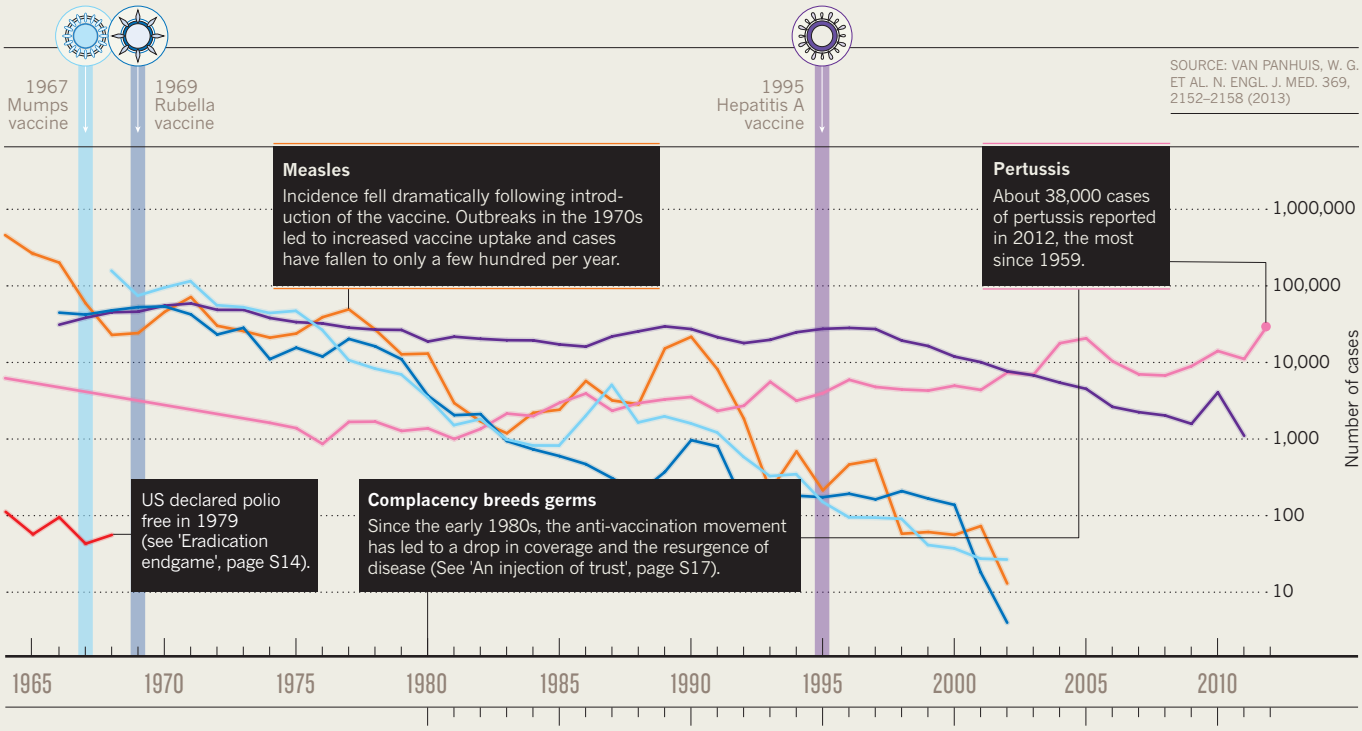
Polio
Crippling viral infection all but eliminated world but for a few countries (see page S14).

Measles
Respiratory infection that can cause body rash. Estimated 1 in every 5,000 people with measles will die from complications.

Mumps
Highly infectious virus causing glands to swell, giving a chipmunk-like appearance. Complications can lead to deafness or aseptic meningitis.

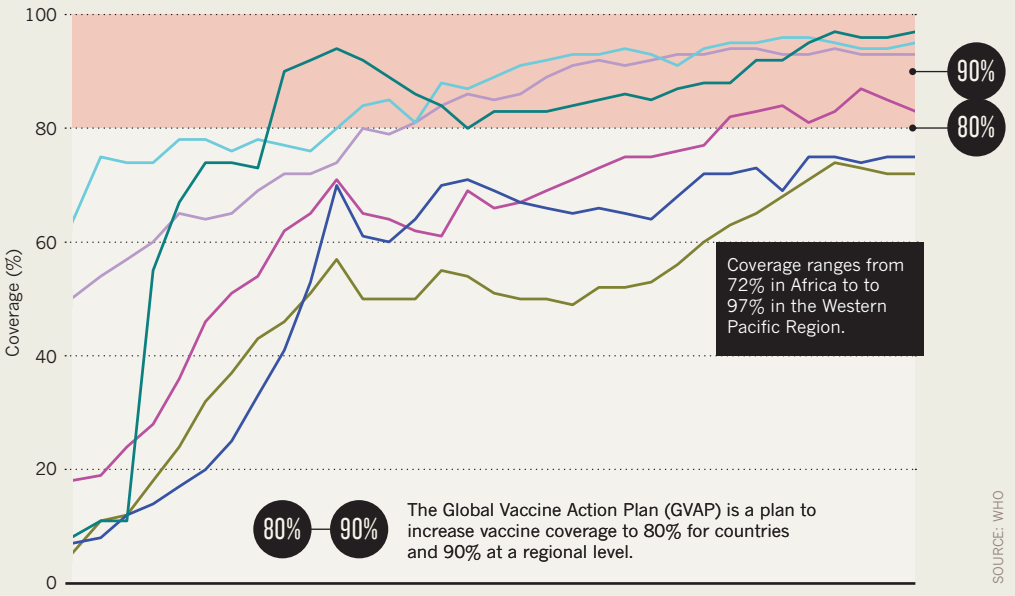
Rubella
If a pregnant women catches the usually mild infection, unborn child has a two in three chance of developing syndrome, including deafness and metal disability.

Hepatitis A
Flu-like viral infection usually contracted by consuming tainted food or water. Illness more severe if liver becomes infected.



THE RIGHT DIRECTION

Since the early 1980s, vaccine coverage has risen rapidly. During 2012, 131 countries achieved ≥90% national DTP3 coverage, and 30% achieved ≥80% DTP3 coverage in every district. Developing programmes to suit each country will help ensure that enough children are being protected against vaccine-preventable diseases (see 'Keeping cool', page S8).



KAREN KASMAUSKI/SCIENCE FACTION/CORBIS

A doctor lifts an AIDS patient in Cambodia. A therapeutic HIV vaccine could be in clinical trials in 2016.

INFECTIOUS DISEASE

Beating the big three

Malaria, HIV/AIDS and tuberculosis are humanity's deadliest foes, and have stymied vaccinologists for centuries. New technology and ideas could finally make a difference.

KATHERINE BOURZAC

Vaccines have conquered so many pernicious diseases that their success has started to seem inevitable. But three of the deadliest infectious diseases — two of them ancient and one that emerged as a threat just 30 years ago — have so far defied vaccine developers.

There are no examples of natural immunity to any of these three diseases — malaria, tuberculosis (TB) and HIV/AIDS. Those who don't die of AIDS or active tuberculosis must live with HIV or latent TB. And those who survive malaria don't develop long-term immunity: they can be infected by the parasite again and again. Without natural models of immunity to work from, vaccinologists have had to develop new strategies. Now these efforts are starting to pay off, leading to cautious optimism that the bacterium, parasite and virus responsible for these diseases might not be as invincible as they seem.

The technology and methods that underpin vaccine research for each of the three pathogens involved have all benefited from the intensive global-health efforts that followed the emergence of AIDS. Funding organizations such as the Bill & Melinda Gates Foundation and the Global Fund to Fight AIDS, Tuberculosis and Malaria began pumping money into research on these killer diseases around the year 2000.

Although new drugs and more ambitious prevention efforts have lessened their toll, the long-term solution to these diseases is prevention. "A vaccine is the ultimate medicine: you don't have to get sick, and they're cheap," says Dennis Burton, an HIV researcher at the Scripps Research Institute in La Jolla, California. Indeed, the economics of vaccines are compelling. For example, about US$2 billion is spent each year on preventing and treating malaria; but if a vaccine were available for US$10 a dose, it would cost only about US$300 million each year to vaccinate every newborn in the countries where the disease is endemic, says Adrian Hill, who studies malaria vaccines at the Jenner Institute in Oxford, UK.

Malaria vaccines under development will target the parasite at every stage of its complex lifecycle, and researchers are optimistic about prospects for eradicating the disease. New genetic analysis methods are finally shining a light on people's different responses to TB and might help to bring down the costs of clinical trials. Meanwhile,

➲ NATURE.COM
For more on malaria, tuberculosis and HIV/AIDS:
nature.com/nrmicro

basic science has shown up some of HIV's weak points, and a vaccine that cures monkeys of simian AIDS is being developed for the clinic.

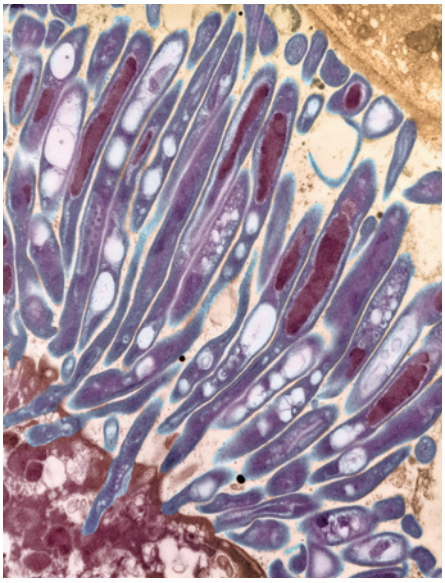
MALARIA: TARGETING A PARASITE

In 2013, there was very good news on the malaria vaccine front. In October, London-based pharmaceutical giant GlaxoSmithKline (GSK) announced that it will apply to the European Medicines Agency for approval to begin selling its malaria vaccine in 2015. GSK developed the vaccine in partnership with the PATH Malaria Vaccine Initiative, funded by the Bill & Melinda Gates Foundation. The vaccine, called RTS,S, was tested in a late-stage clinical trial in more than 15,000 infants and children at 11 sites in sub-Saharan Africa. After 18 months of follow-up, there were 47% fewer cases of malaria in children aged 5 to 17 months at first vaccination, and 27% fewer cases in infants who were 6–12 weeks old when first vaccinated, than in unvaccinated children. RTS,S is the first vaccine to produce protection against any parasitic disease.

The GSK vaccine works like many existing vaccines. It induces the body to make antibodies, in this case against a protein made by the infectious stage of the malaria parasite. If measured solely in terms of the levels of anti-malarial antibodies that it is can induce, RTS,S is "the world's most potent vaccine," says Hill. It induces antibody concentrations ten times greater than does the hepatitis vaccine.

So why does it protect only 50% of children, at best? The answer lies in the parasite's multi-stage life cycle. "From a vaccine point of view, malaria isn't one disease — it's four," Hill says. Malaria parasites reproduce in mosquito salivary glands in one form; travel through the human blood stream in another; replicate in the liver as a third; then infect red blood cells and reproduce again. RTS,S targets only the infectious stage — the single-celled sporozoites that are injected into the body by a feeding mosquito. To prevent disease, there needs to be enough antibody in the blood to eliminate every single sporozoite before they reach the liver. "Once it's in the liver, a single parasite can expand by 10,000 to 40,000 times," says Robert Seder, a vaccinologist at the National Institute of Allergy and Infectious Disease in Bethesda, Maryland.

Because a single parasite can do so much damage, vaccines have to have redundancy built in, says Hill. The ultimate malaria vaccine will not just induce the immune system to attack every stage of the parasite in the human body — critically, it will also block reproduction in mosquitoes. A transmission-blocking vaccine will induce the human immune system to make antibodies against the plasmodium's mosquito-borne stage. When people are bitten, mosquitoes will take up these antibodies, which will prevent the parasite from reproducing within the insect.



LONDON SCHOOL OF HYGIENE & TROPICAL MEDICINE/SCIENCE PHOTO LIBRARY

Malaria parasites growing in mosquito salivary glands can be used for an experimental vaccine.

Transmission-blocking vaccines have long shown promise in theoretical models; in 2013, their potential was confirmed in the lab. An intervention that inhibited transmission of a similar plasmodium parasite from mouse to mosquito by just 32% was able to eliminate the disease entirely in populations with low transmission rates.

For other ideas about malaria vaccination, some researchers are turning to the results of a bizarre 45-year-old experiment that shows that when people are bitten by at least 1,000 sporozoite-carrying mosquitoes that have been irradiated to inactivate the parasites, they are protected against malaria for 20 years. Although a vaccine such as RTS,S works by introducing a single malaria antigen, exposing people to the entire sporozoite instead has the advantage of letting the body pick the targets, says Seder.

Using mosquitoes as a vaccine vector is not practical, as it would require researchers to capture and breed millions of the insects and to release them in thousands of places. So entrepreneur Stephen Hoffman has been working since 2003 to bottle the process. His Rockville, Maryland-based company, Sanaria, has developed a process for growing sporozoites in mosquitoes in the lab. Sanaria breeds mosquitoes in clean conditions, feeding them on banked human red blood cells infected with the parasite. After about three weeks, sporozoites develop in the insects' salivary glands. The sporozoites are then irradiated and purified.

Solving the production problem wasn't enough. Injecting the Sanaria vaccine into muscle, which is how most vaccines are given, doesn't work. Looking at Sanaria's work, Seder had the idea of giving the company's vaccine candidate intravenously. A clinical trial in 40 people yielded promising results that were published in August 2013. A group given six doses was completely protected against malaria infection. The Sanaria vaccine went into larger clinical trials in Tanzania and Mali in December 2013. But even if these studies establish the vaccine's effectiveness, that might not be enough. The vaccine has to be given multiple times, intravenously, and Hill is sceptical that this will ever be practical for resource-poor areas. Even in rich countries, he points out, no vaccines are given intravenously.

In one important respect, malaria is easier to study than HIV or TB: vaccine ideas can be tested quickly and inexpensively. People inoculated with an experimental malaria vaccine can be "challenged" with infection by malaria, because it is possible to kill all the parasites. With the help of existing antimalarial drugs, a person will completely recover from malaria. This vaccinate-then-challenge strategy means that malaria trials can enrol fewer people and still get statistically significant results. It's unethical to challenge people with HIV or TB because there is no way to completely eliminate infection by these pathogens. HIV and TB vaccine trials have to be large: success is gauged by calculating whether the natural infection rate in a population has been lowered.

Partly because of the relative ease of trying out new ideas, malaria researchers are optimistic about prospects not just for RTS,S but also for experimental vaccines coming down the pipeline. Seder says he expects there to be a highly effective malaria vaccine within the next ten years.

TUBERCULOSIS: PREDICTING PROTECTION

So far, there are no vaccines for malaria or HIV, but there is one for TB, and it's the most widely used vaccine in the world. The Bacillus Calmette-Guérin (BCG) vaccine — named after the French researchers who developed it by attenuating one of TB's bacterial cousins — was first used in people in 1921.

BCG, though time tested, has major limitations. For reasons that are poorly understood, BCG protects only infants; it is ineffective in older children and adults. Its efficacy also depends on latitude. BCG works better, and protects people at later ages, farther from the equator. Both effects may result from interfering exposure to noninfectious mycobacteria that are closely related to both BCG and TB. These bacteria are more abundant closer to the equator, and while infants are unlikely to have encountered them, children and adults have had more exposure over time.

And so, in spite of the vaccine, TB ranks second only to AIDS in the number of people it kills every year — 1.3 million in 2012. One-third of the world population is infected with the bacterium, though mostly in a latent form that will never cause a problem for most people. So there is a pressing need for a vaccine that will protect older children and adults against TB.

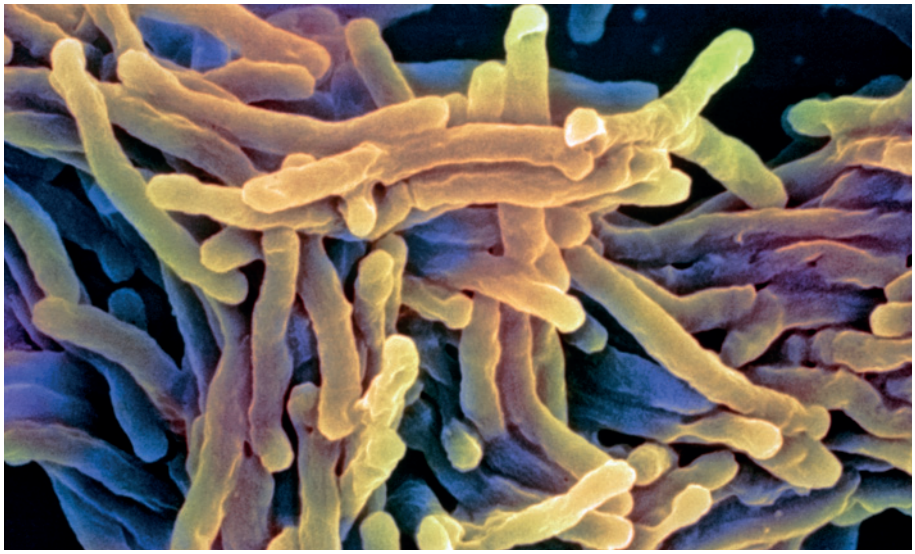
In 2013, researchers completed the first efficacy trial of a novel TB vaccine in infants since 1968, when the last infant BCG trials were done. The trial investigated the vaccine as a post-BCG booster in babies, chosen because they have higher rates of TB infection than adolescents and therefore the trial could include fewer subjects, says Helen McShane, a vaccinologist at the Jenner Institute who was one of the leaders of the trial. But by choosing infants, they may have set themselves too high a bar. "BCG is doing a lot, and it is hard to improve on that," she says. And in fact the new vaccine showed no improvement over BCG alone. But McShane is not discouraged. "It took malaria and HIV researchers a few clinical trials to get to vaccines that show modest efficacy," she says. "We need to keep moving forward, and make sure we learn from things that don't work."

Even more important than improving the infant vaccine is to extend TB protection to the adolescents and young adults who are most likely to be killed by pulmonary TB. The problem is becoming more urgent with the emergence of strains that are resistant to multiple antibiotics, particularly in post-Soviet countries such as Belarus, Ukraine and Kazakhstan. And TB has deadly synergy with AIDS: TB causes one-quarter of all deaths in people with HIV.

The biggest challenge in TB vaccine research is that researchers don't know what immunity looks like. While modestly effective vaccines for HIV and malaria are providing researchers in those fields with promising avenues to pursue, those developing new TB vaccines have almost nothing to go on. The response of the undeveloped newborn immune system to BCG is not a guide to what adult immunity would look like, and the animal models of TB infection are poor. One very basic question is this: how is it that some people can carry the bacteria in latent form for years without getting sick, while others get pulmonary TB? "We're shooting in the dark right now," says Christopher Dye, a TB expert at the World Health Organization (WHO).

Biologists now believe they know how to turn on the lights. To make sure they test only the most promising TB vaccines in future trials, researchers are coming up with new ways of predicting success. One strategy is to challenge people given an experimental vaccine with infection by BCG bacteria, as it's not ethical to infect people with TB. The closely related BCG can act as a surrogate — it's not the same as TB, but watching the immune response to this bacterium could help to guide vaccine development in early clinical trials. The idea, says McShane, is to "challenge vaccinated people with BCG, do a biopsy to study the immune response, redesign the vaccine, then test again."

As interest in TB has grown, so has the ability of biologists to study large networks of genes in both people and bacteria, in order to identify previously invisible markers of immunity and vulnerability. For example, people who live with latent TB — or who are exposed to it but never infected — might have some kind of protective signature that a vaccine could induce in others. This kind of approach — using bioinformatics to parse huge amounts of genetic data for patterns and interconnections — is called systems biology (see "Searching for patterns", page S10). "If ever there was a disease readymade for a systems biology approach, TB is it," says Anthony Fauci, director of the National Institute of Allergy and Infectious Disease.



A. DOWSETT, PUBLIC HEALTH ENGLAND/SCIENCE PHOTO LIBRARY

Large-scale analysis of biomarkers may show up weaknesses in *Mycobacterium tuberculosis* bacteria.

"We need to bring much more effort into biomarker discovery," says Stefan Kaufmann, a TB researcher at the Max Planck Institute for Infection Biology in Berlin. Kaufmann is participating in an international, multi-institution biomarker-discovery study. One branch of the study has enrolled 850 people in South Africa, Ethiopia and The Gambia at the time of their TB diagnosis. The group will also follow about 4,500 of their household contacts — people who were TB negative at the start of the study but are at great risk of infection. Every six months, the researchers are looking closely at gene expression and metabolism in people who are exposed to TB in the home; they hope to find differences between those who go on to develop TB and those who do not. Researchers at Stellenbosch and Cape Town Universities in South Africa are collecting clinical data and storing the samples, which will be analysed by Kaufmann's group and by a team at the Seattle Biomedical Research Institute in Washington.

One goal of this study, says Kaufmann, is to find a biological signature associated with a higher risk of developing the disease so that future clinical trials of TB vaccines could enrol only people from this smaller population who are at higher risk. "This could bring the cost of an early stage trial down from more than US$5 million to less than US$2 million," Kaufman says. He expects the results of this study to be available in two to three years.

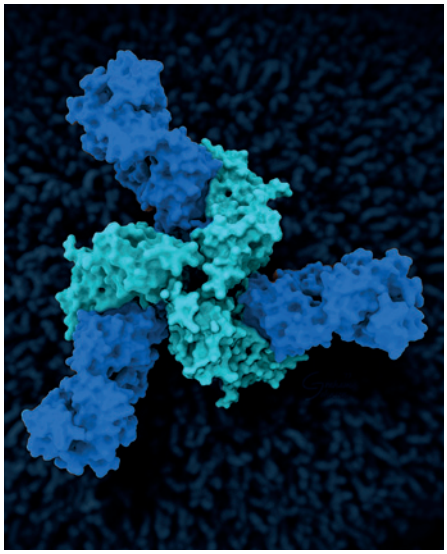
HIV: PORTRAIT OF A PATHOGEN

HIV is responsible for more deaths than any other infectious disease — an estimated 1.6 million in 2012. The virus that causes AIDS was discovered in 1983 at the Pasteur Institute in Paris. It took 20 years for the first HIV vaccine to enter clinical testing, and the news was not good: the first two trials, completed in 2003, showed no effect. Results from three other trials have also been disappointing. In 2007, Merck's Step trial was halted when it was found that the vaccine actually increased the risk of infection in some men (a problem that was traced to the viral carrier used to deliver the HIV antigens); a separate trial of the same vaccine was also halted because of these results. In spring 2013, a fifth trial, using different viral carriers and antigens, was halted early because the vaccine showed no sign of efficacy.

"Without natural models of immunity to work from, vaccinologists have had to develop new strategies."

Against this background of miscues, a 2009 trial that showed modest efficacy is a bright spot. This 16,402-person trial, conducted in Thailand, protected 31% of men and women at 42 months after vaccination. That's not good enough to market the vaccine but the results of the Thai trial provide, at last, a sketch of what immunity against HIV might look like. Now, researchers are trying to learn why the vaccine seemed to work in some people and not others.

A picture is emerging from the data, according to Jerome Kim, an immunologist at the United States Military HIV Research Program in Bethesda, Maryland, and a



GRAHAM JOHNSON, UCSF

New imaging methods show a key HIV protein, the Env trimer (centre), bound to antibodies.

leader of the Thailand trial. For example, vaccinated participants who did not become infected with HIV were more likely than those who did become infected to have antibodies to a particular region of HIV's coating, or envelope, called V2, which seems to help the virus to enter the human immune cells it infects. Other parts of the envelope act as decoys — the body makes antibodies against them, but they do no good. "V2 is tucked away, camouflaged in sugars," says Kim. He also notes that, in the 2013 trial that was halted, the people who were vaccinated did not make antibodies to V2 — a sign that it may be an important part of the virus to target with vaccines.

Some researchers are sceptical about the Thailand trial. The antibodies made by vaccinated people were specific to the strain of the virus targeted in the study, but HIV is a tremendously mutable, variable virus, and any successful vaccine will have to offer broad protection. A successful HIV vaccine will have to induce what are called 'broadly neutralizing' antibodies — those that will react with any strain of the virus, says Burton.

A small fraction of people living with HIV do produce antibodies that neutralize a broad variety of HIV strains. But they don't start to do so until they have been infected for two or three years, at which point the virus is entrenched, and the antibodies cannot eliminate it. People who make these antibodies can still die of AIDS. However, researchers expect that if a vaccinated person is already making broadly neutralizing antibodies when he or she is exposed to HIV, the antibodies could prevent infection.

Inducing these antibodies is a major challenge, made more difficult by the lack of understanding of HIV's structure. Key parts of the HIV envelope — including V2 and other regions that are important for initiating infection — won't crystallize. This means that X-ray crystallography, the primary method for figuring out protein structures, can't be used to create images of them. To solve this problem, Burton and others are enlisting new imaging techniques and modelling software to learn more about which part of the virus the antibodies bind to and how, so that they can be engineered from the ground up.

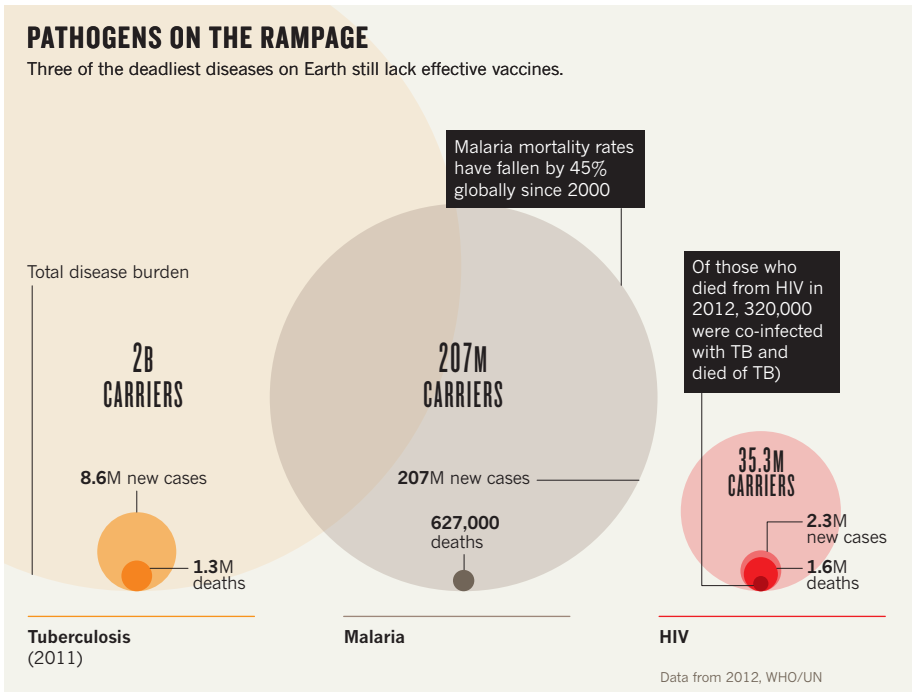
Burton has pioneered the discovery of broadly neutralizing antibodies and the development of the technology needed to study them and their binding sites. In November 2013, using a high-resolution imaging method involving an electron beam and very low temperatures (cryo-electron microscopy), researchers were able to take a picture of one of the most important parts of the virus that until then had been blurry: the three-part envelope protein called the Env trimer.

These pictures give protein researchers somewhere to start. The idea is to engineer a protein that contains the vulnerable region of the HIV envelope, packaged with protein sequences that will help it to hold its proper shape. When exposed to this artificial antigen, a person's immune system would make broadly neutralizing antibodies. Designing such a structure requires sophisticated computer models that can predict what sequence of amino acids will fold into the proper shape — a technology that now exists. Nevertheless, Burton suspects this endeavour will take time; the first such structural vaccines probably won't work, but researchers will keep testing and improving them in animals until they're ready for the clinic.

These types of engineered vaccine could be used to overcome one of HIV's greatest challenges: its incredible diversity. The key is to move beyond simply making antibodies; there is another branch of the human immune system that needs to be engaged, says Louis Picker, who is developing an HIV vaccine at the Oregon Health & Science University in Portland. Picker specifically cites the need to activate memory T cells, which remember and kill pathogens. No existing vaccine works through T-cell memory, says Picker, but researchers doubt whether any HIV vaccine can work without engaging it.

Picker's idea was recently tested against the virus that causes AIDS in monkeys — simian immunodeficiency virus (SIV). The vaccine used in the study uses another pathogen, called cytomegalovirus (CMV), to attack the immunodeficiency virus. CMV itself leads to a lifelong, but usually harmless, infection. The Oregon researchers engineered a CMV carrier that makes SIV antigens. In monkeys, the vaccine version of CMV activated the immune system not just to make antibodies but also to generate memory T cells that recognized SIV. Picker gave the vaccine to monkeys with persistent SIV, and the infection was cleared, an effect that he attributes to memory T cells. The protective effect should last as long as the CMV infection persists — that is, a lifetime. Picker is now developing a version of the vaccine designed to target HIV, and he hopes to start clinical trials in 2016.

According to Picker, a successful AIDS vaccine will probably involve combining his approach with structural antibodies such as those Burton is trying to make. "It will take time," says Burton, "but an HIV vaccine is going to come." ■



Katherine Bourzac is a freelance science writer based in San Francisco, California.

PALLAVA BAGLA/CORBIS

A village nurse carries her characteristic 'vaccine bag', an insulated case that is crucial for keeping vaccines at the right temperature, in Vailankanni near Tamil Nadu in India.

LOGISTICS

Keeping cool

Extreme temperatures damage vaccines. Efforts are underway to find better ways to deliver the goods.

NEIL SAVAGE

One hot November afternoon in the West African country of Benin, a line of rural villagers takes shade beneath trees as they wait their turn for a shot. Vaccinators have travelled here, and to other villages in the Banikoara district, on bicycles, trucks and motorbikes bearing insulated containers holding a vaccine against a strain of meningococcal meningitis, which is endemic to this part of the world.

This vaccination campaign in 2012 was different from those that went before it: none of the vaccinators were toting the heavy ice packs used to keep vaccines between 2 °C and 8 °C as recommended by the World Health Organization (WHO). The vaccine, MenAfriVac, was approved for use even after being stored at up to 40 °C for as long as four days.

The ability to transport doses of a vaccine outside the so-called cold chain — the series of refrigerators, refrigerated trucks, and ice-chilled carriers that keep the medicine between 2 °C and 8 °C — will lower the cost of vaccination, improve the delivery of vaccines in the developing world, and give health-care workers greater flexibility in reaching those in need, says Simona Zipursky, a public health specialist in the WHO's Expanded Programme on Immunization. No longer would healthcare workers have to travel to the nearest city overnight just to freeze ice packs, and they could stay in the field longer without having to throw away vaccine that had expired from the heat. "Four days isn't four years, but it opens the pathway," Zipursky says.

Maintaining the cold chain is a major challenge to the goal of delivering vaccines to everyone who needs them, particularly in the developing world. So researchers are looking for new vaccine formulations and delivery systems that don't depend on such a narrow range of temperatures. At the same time, they're working on ways to improve the cold chain, with high-tech containers for transporting vaccines and information technology to monitor cold storage.

BREAKING THE CHAIN

MenAfriVac was the first vaccine to be approved for use outside the cold chain. It was developed in a collaboration between the WHO and PATH, the Program for Appropriate Technology in Health, an international not-for-profit organization based in Seattle, Washington. Immunization specialists have long known that the standards for vaccine expiration were very conservative, Zipursky says. Vaccine makers generally run accelerated stability studies: stress tests in which they expose the medicine to high temperatures to see when it starts to break down. The collaboration added a few additional tests to measure various ways in which the chemistry of this vaccine could change to render it useless, and decided it would still be safe and effective after up to four days at 40°C. "In reality," Zipursky says, "we probably have somewhere near a few weeks."

Initial results suggest that MenAfriVac has greatly reduced the incidence of meningitis. A study in Chad during the 2012 infection season found only 2.5 cases of this strain of meningitis per 100,000 people where the vaccine had been distributed, compared to 43.8 cases per 100,000 where it had not been distributed.

Different vaccines vary in their ability to tolerate high temperatures, Zipursky says. The collaboration is looking at the temperature tolerance of other vaccines, including those for cholera, hepatitis B and yellow fever. Running these studies can be costly: manufacturers don't necessarily have all the needed data on shelf life, and "it's not as fast a process as we would like," she says.

Heat isn't vaccines' only enemy. "Freeze damage may potentially be a greater issue than heat damage to vaccines," says Debra Kristensen, who leads PATH's vaccine technologies group. Many vaccines contain adjuvants: chemical compounds such as aluminium salts that stimulate a better immune response. If a vaccine freezes, the aluminium compounds clump together and become ineffective, rendering the vaccine less potent. A 2007 analysis by PATH of several studies found that between 14% and 35% of vaccine shipments were exposed to sub-zero temperatures at one point during shipping or storage. Analysis of a smaller group of six studies found that, in multiple rounds of shipping and storage, nearly all vaccine shipments examined were exposed to freezing temperatures at some time.

"Essentially, the more you look for freeze exposure, the more you'll find it," says Dipika Matthias, a public health specialist at PATH

SSPL/GETTY IMAGES

A state-of-the-art vaccine carrier keeps its cargo cool for longer.

and an author of the study. So researchers at PATH are experimenting with adding chemicals, such as glycerin, to act as an antifreeze in vaccines for polio, hepatitis B and diphtheria-pertussis-tetanus. The additives are considered nontoxic, but adding them to vaccines does require new rounds of safety testing to get regulatory approval. Because of the time and cost involved in such testing, Kristensen says it makes more sense to add stabilization agents to new vaccines under development rather than to existing ones. "It's an expensive process," she says."

Another approach is to move away from liquid vaccines entirely. Vaccine dried to a powder is more stable and doesn't require refrigeration. Here, vaccine makers can borrow technology that's been used in the food industry for decades, such as freeze-drying. This process freezes the vaccine quickly enough to minimize clumping of the adjuvants. The downside — in addition to the higher manufacturing cost — is that the dried vaccine needs to be mixed with liquid again before it can be injected. In areas with limited clean water and sterilization facilities, the reconstitution process could introduce contamination, Kristensen says.

A newer approach for vaccines, although still an old technology, is spray drying. The vaccine is passed through a nozzle and shot out as a fine spray of tiny droplets into a drying chamber filled with inert, heated gas. In addition to stabilizing the vaccine, the process also allows manufacturers to control the size of the particles, opening up new methods to deliver the vaccine. The right-sized particles can be easily absorbed through mucous membranes, so the vaccine could be inhaled instead of injected.

Diane Griffin, an immunologist at Johns Hopkins Bloomberg School of Public Health in Baltimore, Maryland, tested a powdered measles vaccine on a group of macaques. The powder was created with a spray-drying process developed at the University of Colorado, Boulder, by biotechnologist Robert Sievers. The powder was either applied on a mask strapped to the monkey's face or puffed into its nose with a squeezable bulb. The inoculation succeeded in protecting the monkeys against measles and caused no ill effects.

The powdered vaccine has since gone through a phase I clinical trial in India, where it was tested for safety on a group of already immunized adults. Griffin says the next stage is to test it in infants to see whether it promotes as effective an immune response as an injected vaccine. If it does, "it would make large scale immunization campaigns much easier," she says. "Not only are needles and syringes and the cold chain eliminated, but the vaccine comes in small, single-dose capsules that greatly reduce the volume for shipping and storage."

The same approach could be applied to vaccines for other diseases, such as rubella and mumps. Unfortunately, Griffin says, there are hurdles that have nothing to do with the science; researchers have been unable to secure funding to continue studying the powdered measles vaccine. "The vaccine community is very reluctant to do the testing and navigate the regulatory hurdles required to replace a cheap, successful vaccine with something even better," she says.

STRONGER LINKS

For the time being, vaccinators are relying on liquid vaccines. Researchers at Global Good, a collaboration between the research laboratory Intellectual Ventures, of Bellevue, Washington, and the Bill & Melinda Gates Foundation, are developing a vaccine carrier designed to keep medicine cold while surviving journeys along bumpy roads in areas without electricity.

The carrier is essentially a high-tech version of a thermos: two stainless-steel cylinders with a vacuum in between for insulation. The cylinders are corrugated, increasing the surface area, so that heat from the outside has to follow a much longer path to reach inside the container. It's wrapped in thin, multiple layers of aluminium foil that act as an insulator and reflect heat from the container. "We have specifically designed it to fight the three ways that heat moves: convection, conduction, and radiation," says Geoff Deane, vice president at Intellectual Ventures. Only 1 W of heat energy leaks into the device, he says, compared to 30–50 W for the best insulating styrofoam carriers. Ice in separate plastic containers inside the carrier keeps it cool but doesn't come into direct contact with the vaccine, and keeps the vaccine fresh for over a month. Simple, battery-powered electronics record the temperature being maintained, while a GPS device tracks the carrier's location. All this information can be transmitted via SMS message. "Once a day it phones home and reports that data," Deane says. The team is performing field trials of the carrier in West Africa and a manufacturing partner is preparing to produce the device. Deane expects it will be ready for sale to vaccine distributors by mid-2014.

Such monitoring and tracking technology is already in use across the cold chain, says Liz Peloso, who heads PATH's Better Immunization Data Initiative, a new five-year, US$19.5 million project funded by the Gates Foundation. For instance, many health centres have US$20 electronic tags that monitor temperatures in storage refrigerators, and then send the data to a central repository. But these technologies are not currently used to their full potential, says Peloso.

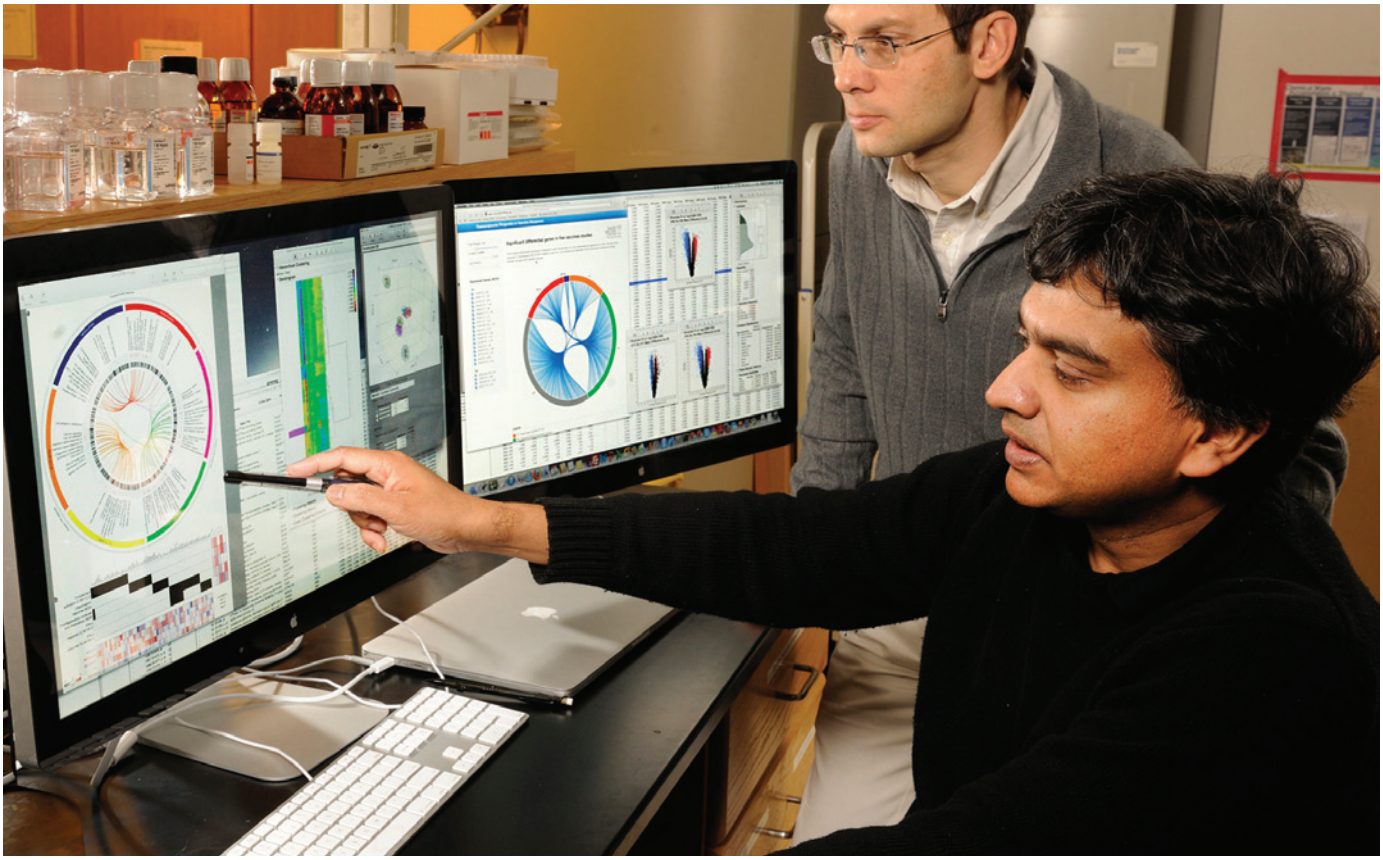
In many cases, she says, workers at the local health centre are not privy to the information, which does not reach a central health district until weeks later. Or one health centre might be out of a vaccine while a neighbouring centre a few kilometres away has vials it can't use before they expire, but there's no way to share that information and, therefore, the extra vaccine. There needs to be a culture change that encourages local workers to identify and solve problems, Peloso says; if a tag records that a refrigerator temperature is going out of range at certain times, the local workers should know to check whether there's a problem with the power supply or someone is leaving the door open. Such simple responses usually aren't happening, she says. The initiative's aim is to develop protocols that take advantage of collected data to answer the question: "How do you turn the data points into information that somebody can use?"

"Maintaining the cold chain is a major challenge to the goal of delivering vaccines to everyone who needs them."

The Better Immunization Data Initiative will launch its first project in Tanzania later in 2014, then start adding other countries where the infrastructure — electricity and communications — is stable enough to take advantage of the technology.

Ultimately, protocols designed to improve immunization could also spill into other areas, such as perinatal care, AIDS treatment and nutrition. "If you can make these things more efficient and effective," Peloso says, "you can really make a difference in how a country's health system operates." ■

Neil Savage *is a science and technology writer based in Lowell, Massachusetts.*



JACK KEARSE/EMORY UNIVERSITY

Emory University's Bali Pulendran and Dmitri Kazmin use systems biology to look for the 'molecular signatures' of the antibody response.

DRUG DEVELOPMENT

Searching for patterns

Tapping into big data could inform better vaccine design.

BY TOM PAULSON

Immunization is often hailed as one of medicine's greatest triumphs. Yet its success has been largely accomplished without fully understanding exactly how it works. Take, for example, one of humanity's best vaccines — YF-17D, which protects against yellow fever. A single immunization with this vaccine provides decades of almost complete protection, but until recently its mechanism was shrouded in mystery. It worked, but "nobody really knew why," says Bali Pulendran, an immunologist at Emory University in Atlanta, Georgia.

That mystery can be traced back to the origins of the yellow fever vaccine. YF-17D was developed in the early twentieth century by Max Theiler, who in 1951 won the Nobel Prize in Physiology or Medicine for his work. Theiler relied on methods that barely departed from those used by Edward Jenner in his discovery of the smallpox vaccine in the eighteenth century. "Vaccine development has been a trial and error process," says Pulendran. "We really don't understand the basic mechanism of how vaccines produce immunity."

The traditional approach to developing vaccines entails identifying the causative agent, killing or crippling it (for example by heating or irradiating it) and then injecting the inactivated virus or bacterium into animals or people, to produce an immune response — a sequence described as 'isolate, inactivate and inject'. There are some more sophisticated variations on this theme, such as producing only the immunogenic proteins using recombinant genetics rather than inactivating a whole virus. But the empirical approach to vaccine development can hit a wall when confronting the trickiest pathogens.

"The search for vaccines against several incurable diseases, including AIDS, malaria, tuberculosis (TB) and dengue fever, has largely failed," says Rafick-Pierre Sékaly, chief scientific officer at the Vaccine & Gene Therapy Institute of Florida in Port St Lucie, and his colleague Lydia Trautmann. This failure demands a new, more comprehensive and rational strategy.

Scourges such as HIV, TB and malaria are caused by microbes that have evolved to evade and undermine the immune response (see 'Beating the big three, page S4). "I don't think we will be able to develop vaccines against these three diseases without understanding a lot more about how the immune system works," says Alan Aderem, an immunologist and president of Seattle Biomed in Washington, a non-profit organization that focuses on infectious disease research. Aderem is pursuing a less haphazard approach — called systems biology — that he and many other researchers are convinced will dramatically improve vaccine discovery and development[1].

TAMING THE DATA TORRENT

Systems biology is often described simply as the marriage of high-throughput computation and biological research, with the goal of sifting through massive datasets to look for emergent, often unanticipated, properties of genes, proteins or other factors as they interact in a cell

or organism. The aim is to measure a dynamic network of multiple biological interactions simultaneously without having to know in advance which single variable or process to focus on. Systems biology shows promise as a powerful strategy for dealing with the ever-increasing torrent of biological information. Proponents of systems biology hope that it will help researchers to identify hidden and complex interactions that can reveal new insights into what drives the immune response and find new targets for candidate vaccines.

In 2005, Pulendran and his colleagues chalked up the first big vaccinology win for systems biology when they used the approach to solve the mystery of the yellow fever vaccine. First, they vaccinated individuals with YF-17D. Next, they collected blood samples over time and analysed them to compare gene activity to immune response. What emerged was a network consisting of some 100 genes; this allowed the researchers to identify five key proteins (toll-like receptors) that trigger innate immune activity, which usually provides a rapid, non-specific response to invading pathogens[2]. "That was the first demonstration of a vaccine mediating its effects by triggering such receptors in the innate immune system," Pulendran says. Follow-up studies allowed the researchers to predict the magnitude of the antibody and T-cell responses to the vaccine, and hence its efficacy[3].

More recently, Pulendran's analysis of the biological response to the yellow fever vaccine has revealed a key insight into the vaccine's mechanism. It turns out that the *GCN2* gene, which encodes a protein that is expressed in response to amino-acid deprivation, also promotes the T-cell response — involving 'CD8' or 'killer' T cells — that makes the yellow fever vaccine so effective[4]. "The GCN2 link to immunity was not appreciated," he says. "This is a good example of how the systems approach can give critical new insights you could not have anticipated."

Pulendran's analysis of the yellow fever vaccine was widely regarded as proof of concept for the systems biology approach. The National Institutes of Health (NIH), for example, cited the paper in 2009 in support of its US$100 million Human Immunology Project Consortium, which focuses on applying systems biology to a broad spectrum of questions in human immunology. But Pulendran's analysis was still a largely descriptive study of a vaccine that had already been proven to be effective. In that sense, this work offered only indirect evidence that systems biology could predict whether a new vaccine would offer protection. What are most needed to advance vaccine development are predictive findings.

Aderem, who worked with Pulendran on some of the YF-17D studies, says the findings support his belief that systems biology offers the best hope for deciphering the black box of immunity. "One of the clinical signs of madness is doing the same thing over and over and expecting a different result," he says. And when it comes to vaccine development, "we need a new approach."

PICKING OUT PATTERNS

Aderem, Pulendran and others say we're on the verge of entering a new phase of the study of immunological genomics — a more rational, systematic method of studying immunity and developing vaccines. Yet only a dozen or so labs worldwide are applying the systems approach to vaccine development.

Until recently, the field was stymied by lack of funding as well as by scepticism from scientists who regarded it as unproven and as a solution in search of a problem. One leading critic of systems biology — Nobel laureate and biologist Sydney Brenner — contends that it suffers from what might be called the 'Big Data' delusion. Brenner has repeatedly criticized the anti-reductionist approach of systems biologists because he believes it furthers the practice of collecting biological data without committing to a clear hypothesis or theory of action: "We are drowning in a sea of data and thirsting for knowledge," he argues. "Most biology today is low input, high throughput, no output."

The point, which others besides Brenner have also made, is that too many biologists today are merely sifting through reams of data hoping for magical conclusions. "There seem to be a lot of people around who think that if you measure absolutely everything, somehow the truth will jump out and punch you on the nose," says Nobel laureate and biochemist Tim Hunt. "Experience suggests that it's more of a recipe for confusion."

"The systems approach can give critical new insights you could not have anticipated."

But the yellow fever vaccine analysis showed that systems biology can offer new ways to manage and probe massive datasets, and was therefore a watershed moment for the field. The NIH initiative, Aderem believes, is a sign that scepticism is on the decline. Critics of systems biology, he says, tend to not give enough weight to the the potential power of this approach to identify patterns and networks at work within the cell without having to commit to a specific theory of action or starting hypothesis. Systems biologists, according to Aderem, are not testing the mechanism of a specific antigen or protein; rather, they are looking across the hundreds or even thousands of interactions of different kinds that comprise the immune response to identify a pattern of gene or protein behaviours that hint at basic mechanisms. "It is an unbiased approach to trying to understand a biological system, starting with no preconceptions," says Daniel Zak, a principal scientist at Seattle Biomed who is working with Aderem as well as researchers at the University of Cape Town, South Africa, to try to figure out how *Mycobacterium tuberculosis* infection moves from a non-disease state known as latency to full-blown disease.

Zak's study began in 2010 in collaboration with a team led by Willem Hanekom, director of the South African Tuberculosis Vaccine Initiative. The researchers recruited 6,000 adolescents, half of whom were infected with latent TB. Blood was collected from these adolescents every six months. After two years, 50 of the 6,000 adolescents had developed the disease. The Seattle–Cape Town team is using systems analysis techniques to identify and track changes in gene expression and protein activity in the cells of 150 adolescents — some who developed the disease and some who did not. The scientists have been sifting through the blood samples, looking for any odd patterns. The first clue may come from a novel chain of events carried out by white blood cells. Or it might be a unique pattern of protein–protein interactions, or gene activity. In this case, the first signature of TB disease found by Zak's team turned out to be a particular pattern of gene activity.

"We are trying to identify which genes are turned on in the blood of people who progressed to active disease," Zak says. "We are seeing predictive changes." That is, the researchers have found that this unique pattern of gene activity indicates that a person infected with latent TB is progressing to active disease. These biomarkers, he says, could lead to the development of better drugs or a better TB vaccine candidate by identifying multiple key targets within these networks.

"The problem with drugs is they usually have a single target," Aderem says. "If we can hit an entire network, or critical nodes in a network, it's much harder for the bug to get around the treatment."

Pulendran's team has used systems biology to assess the seasonal influenza vaccine for any signatures that might predict an antibody response[5]. The team compared two flu vaccines — a trivalent inactivated vaccine and a live attenuated vaccine — and found signatures that predicted the human antibody response to the vaccine. Ultimately, Pulendran says, systems biology could help researchers to identify a universal biomarker that predicts the antibody response and reduces much of the guesswork that currently plagues the seasonal preparation of the influenza vaccine. "That would be tremendous advance." ■

***Tom Paulson** is a freelance science writer based in Seattle, Washington.*

1. Rappuoli, R. & Aderem, A. *Nature* **473**, 463–469 (2011).
2. Querec, T. *et al. J. Exp. Med.* **203**, 413–424 (2006).
3. Querec, T. *et al. Nature Immunol.* **10**, 116–125 (2008).
4. Ravindran, R. *et al. Science* doi: 10.1126/science.1246829 (2013).
5. Nakaya, H. I. *Nature Immunol.* **12**, 786–795 (2011).

IMAGINECHINA/CORBIS

Bottles of a Chinese-made vaccine against Japanese encephalitis.

PRODUCTION

Vaccines from the East

China is poised to become a major global vaccine maker, but first it must overcome serious problems with quality control.

PRIYA SHETTY

In 2007, Zheng Xiaoyu, head of China's State Food and Drug Administration (SFDA), was found guilty of corruption and swiftly executed. To the rest of the world, Zheng's punishment might seem extraordinarily severe given that his crime was taking bribes of 6.5 million yuan (US$1 million) in exchange for approving substandard medicines. For China, however, this move was a clear sign of its determination to build its reputation as a key player in global health.

Now, the country may be seeing this brutally enforced determination bear fruit. In October 2013, a Chinese-made vaccine for Japanese encephalitis — a viral brain infection spread by mosquitoes that is similar to West Nile fever and prevalent in South-East Asia — became the first Chinese drug to have its safety and quality endorsed by the World Health Organization (WHO). Every year the Japanese encephalitis virus infects as many as 50,000 children under 15 years old, killing up to 15,000, yet there are no antiviral treatments. The SFDA — renamed in April 2013 as the China Food and Drug Administration (CFDA) — was instrumental in securing the vaccine's approval, which allows United Nations (UN) agencies to use it in vaccine programmes. Buoyed by this success, China is already lining up more vaccines for WHO approval, including vaccines against flu, polio and rotavirus, according to a spokesperson from the CFDA.

This landmark event has been welcomed by many who believe that China's capacity to produce large numbers of vaccines cheaply means that millions more people can be immunized. The WHO's director-general, Margaret Chan, said: "There is a huge potential for vaccine manufacture in China and we hope to see more and more Chinese vaccines become WHO prequalified. The whole world will benefit."

➲ NATURE.COM
For some of the latest research from China, go to:
nature.com/nchina

China has more than 30 domestic vaccine manufacturers that together produce 49 vaccines against 27 diseases. The country's annual manufacturing capacity is nearly a billion doses — about a fifth of Europe's vaccine production. But question marks remain over China's future as a world vaccine supplier. Zheng's story, while extremely high profile, is just one of many scandals surrounding China's research reputation. In the past few decades, the country has seen countless cases of unethical trials, corruption in hospitals and pharmaceutical companies, and counterfeit, substandard or tainted medicines. Despite a renewed commitment to high-quality research and increased funding, China is still failing to tackle these inadequacies.

RED FLAGS

Chinese spending on research and development (R&D) has grown by 20% per year since 1999 and now exceeds US$100 billion per year. China is likely to have more research papers published this year than the United States, according to the Royal Society in London[1]. It is already home to 25% of the world's R&D workforce, according to the UK innovation charity Nesta. However, in a report published in October 2013, Nesta warned[2] that the rise in the quantity of Chinese research "has not yet been matched by similar leaps in quality."

This general trend certainly applies to pharmaceutical R&D. Indeed, China has a poor track record in drug production and clinical trials. For example, in clinical trials conducted in China in 2006 for the blood-thinning drug apixaban (Eliquis), the US Food and Drug Administration found that some patients were given the wrong drug, the trial was run poorly and in violation of good-practice guidelines, and serious side effects were not reported. There have also been cases of clinical trials in which participants have either been coerced into the trial or not told of potential drug risks, and have had to pay for medical treatment for side effects[3].

The growing presence of multinational pharmaceutical companies has helped to increase China's capacity to produce drugs, but those companies have had a rough ride. In 2013, for example, GlaxoSmithKline's China office was embroiled in scandal amid accusations of bribing Chinese doctors and government officials[4], and it later emerged that Sanofi's China branch is also being investigated for bribing Chinese doctors. Several other global pharmaceutical companies with a Chinese presence are also under scrutiny for similar alleged wrong-doing.

China is also notorious for producing low-quality or counterfeit medicines, including antimalarial drugs[5]. And in 2008, powdered baby milk products contaminated with melamine left 296,000 children sick, causing a major scandal[6]. "For a country as big as China, if it cannot even manufacture infant formulas

that all its citizens can trust, the chance that it can become an international supplier of drugs and vaccines is very slim," says Jack Zhang, head of the China programme at PATH, a non-governmental organization based in Seattle, Washington.

All these concerns raise red flags over China's ability to become a major vaccine producer. Quality is "a critical issue", says Seth Berkley, chief executive of the GAVI Alliance, based in Geneva, Switzerland, which works to ensure broader worldwide access to vaccines. "You are giving the vaccine to healthy children and you've got to believe that what is in that vial is what's advertised, and that it's completely safe."

LONG MARCH TO QUALITY

The introduction of China's vaccine against Japanese encephalitis required international funding[7]. Researchers at the Chengdu Institute of Biological Products (CDIBP), a subsidiary of the China National Biotec Group (CNBG), discovered the vaccine in 1988. But development of the vaccine for the global market began only in 1998 when PATH joined forces with the CDIBP — funded by US$35 million from the Bill & Melinda Gates Foundation.

The collaboration "established reliable methods of diagnosing and tracking the disease to help countries understand it, prioritize it, and focus on prevention efforts in regions where children are most at risk," says Kathy Neuzil, director of the Vaccine Access and Delivery Program at PATH. Improved disease surveillance and clinical trials were introduced to establish the vaccine's immunogenicity and safety. The culmination of this effort, says Neuzil, was the design of a new manufacturing facility to ensure "high-quality, adequate, stable and affordable vaccine supply." Only then, in 2011, did the WHO deem China's SFDA to be a functional regulatory authority for vaccines. This was a crucial step because to receive WHO approval for a vaccine, the manufacturing country must have a national agency seen to be able to monitor production and provide regulatory oversight.

Even so, China's vaccine manufacturing sector is by no means ready to go global. Xiaoming Yang, chief executive of the CNBG, acknowledges that China's familiarity with international practices is hazy. "Chinese manufacturers will face lots of challenges," he says, including "a lack of knowledge of international market regulation and lack of experience in conducting overseas clinical trials."

To improve international relations, China must attract overseas talent back to China "to play a critical role in bridging local and international practices," says Zhang. Its capacity to undertake robust clinical trials is still poor, he says, and he urges researchers to follow good clinical-practice guidelines "to foster more rigorous ethical standards for clinical study."

These barriers make it unlikely that China will become a significant international supplier of drugs and vaccines "in the foreseeable future," says Sun-Wei Guo, a professor of obstetrics and gynaecology at Fudan University in Shanghai. A key challenge, adds Guo, is that "in a country where there is a lack of free flow of information, talent and capital, where accountability exists only on paper, and where all major decisions are made by officials who have little incentive to be innovative other than to keep their jobs, the quality of any mass-produced product is predictably inferior."

SAFEGUARDING STANDARDS

It is on this issue of quality control that China's reputation as a vaccine supplier ultimately rests, as failure to maintain standards could result in WHO approval being rescinded. Approval "is a stringent process so the WHO can be confident that the product meets international standards," says David Wood, who heads vaccine regulation coordination in the WHO's Health Systems and Innovation Cluster.

STRINGER SHANGHAI/REUTERS/CORBIS

Workers empty packets of contaminated milk powder in Guangdong province.

The WHO takes this matter seriously, and some Indian vaccine suppliers to GAVI have lost their prequalification status because quality control had fallen short of previous levels. In 2012, the WHO revoked its approval of an oral polio vaccine made by Panacea Biotec, one of India's largest makers of generic drugs[8].

Yang contends that the Chinese drug-making industry is trustworthy, however, and that the widely reported scandals are anomalous. Those events, he says, "do not represent the mainstream of China's pharmaceutical industry. We have established a complete regulatory system from clinical development to market launch."

Berkley, who has developed strong working relationships with senior public-health officials in China through numerous visits, says that "these scandals haven't only been external, they have also been internal, and there's a lot of anger about that in the country. China's leadership is aware of the problems they have had on quality and will take this seriously." Zheng's execution seems as bold a sign as any of China's determination to succeed.

China's high performance in some sectors of manufacturing, such as microelectronics, shows that it can achieve quality. "We're long past the days when a 'Made in China' sticker would be a sign of instant alarm," says James Wilsdon, professor of science policy at the University of Sussex, UK.

But electronics don't trigger the same societal concerns as food products or vaccines, Wilsdon says. Bribery and corruption scandals such as those that hit China's pharmaceutical industry are an "international manifestation of domestic dynamics," he adds. "If this is happening in global players like GlaxoSmithKline, how much are they happening in large state-owned enterprises? Clearly, far more."

Since 2005, researchers conducting clinical trials in China have been strongly advised to register them in the Chinese Clinical Trial Registry (ChiCTR), which was set up to improve transparency and feeds into the WHO's International Clinical Trials Registry Platform. However, such a system can only function if it has the full support of the research community and regulatory industry. By December 2013, only 3,927 trials had been registered, which researchers at the ChiCTR say falls far short of the several thousand trials per year estimated to take place, based on the number of published studies. One positive sign is that the CFDA made the registration of clinical trials mandatory in September 2013.

But until there is concrete action and clear signs of improvement, sceptics such as Guo will remain unconvinced. "There are a lot of talks, and even a lot of meetings, but not a lot of actions, let alone outcomes," he says. "The decision-makers should understand that when it comes to supplying quality drugs and vaccines, political mumbo-jumbo won't work." ■

***Priya Shetty** is a freelance science writer based in Brighton, UK.*

1. *Knowledge, Networks and Nations: Global Scientific Collaboration in the 21st Century* (The Royal Society, 2011).
2. Bound, K. *et al. China's Absorptive State: Research, Innovation and the Prospects for China–UK Collaboration* (Nesta, 2013).
3. Cyranoski, D. *Nature* **435**, 138 (2005).
4. www.bbc.co.uk/news/business-24637195.
5. www.theatlantic.com/china/archive/2013/06/fake-fake-drugs-from-china-whats-stopping-a-cure-for-malaria-in-africa/276750.
6. http://news.bbc.co.uk/1/hi/7720404.stm.
7. *Case Studies for Global Health* (Alliance for Case Studies for Global Health, 2009).
8. www.who.int/immunization_standards/vaccine_quality/delisting_opv_panacea/en.

AGRON DRAGAJ

Female vaccinators — often the only ones allowed to speak to mothers or enter a child's home — wait outside a house in Afghanistan.

POLIO

The eradication endgame

Researchers are developing a strategy that could put an end to polio forever.

BY CASSANDRA WILLYARD

In 1988, scientists around the world launched a massive effort to eliminate polio, a disease that can cripple and kill. The Global Polio Eradication Initiative (GPEI) has since made great progress: the number of polio cases has fallen by more than 99%, from an estimated 350,000 cases in 1988 to around 400 in 2013. And in January, India, once a stronghold for polio, celebrated an important milestone: three years with no new cases. Yet poliovirus stubbornly persists in Nigeria, Afghanistan and Pakistan, where violence, politics and mistrust have hampered eradication efforts. Indeed, in early 2014, Kabul saw its first case of polio since 2001. In 2012, the GPEI issued a dire warning: "Polio eradication is at a tipping point. If immunity is not raised in the three remaining countries to levels necessary to stop poliovirus transmission, polio eradication will fail."

In chess, the final moves must be carefully planned, as one mistake can let your opponent gain the upper hand. It's the same with the polio endgame. Violence has made delivery of the vaccine nearly impossible in some regions. In others, fear and mistrust have led parents to refuse to have their children vaccinated. But there is another, seldom discussed, obstacle to eradication: in rare cases, the live, attenuated (weakened) virus in the oral polio vaccine (OPV) can mutate and spark polio outbreaks.

In April 2013, the GPEI presented a new strategy to wipe out polio — not only the wild virus, but also polioviruses derived from OPV. The plan is to introduce inactivated polio vaccine (IPV), which contains killed virus, in the 124 countries that rely on OPV by 2015. A more effective oral vaccine will then be used to eliminate the last pockets of virus. Once the world is free of polio, the oral vaccine can be phased out entirely. Introducing IPV in so many countries will pose a "major challenge", says Elizabeth Miller, an epidemiologist who chairs the polio working group of the Strategic Advisory Group of Experts (SAGE) on Immunization. "On the other hand, it offers huge rewards in terms of progress towards eradication."

SABIN VS SALK: THE REMATCH

Poliovirus replicates in the human gut and spreads through sneezes or coughs, or when someone comes into contact with infected faeces. Most people who contract polio develop only mild symptoms, if any. But in roughly 1 out of 200 infected individuals, the virus invades the nervous system and causes permanent paralysis. If the muscles that control breathing are paralysed, the disease can be fatal.

The fight against polio hinges on the two vaccines, IPV and OPV. IPV, an injectable vaccine invented by Jonas Salk and introduced in 1955, contains virus that has been bathed in a formaldehyde solution; this killed virus cannot replicate or cause paralysis. OPV, developed by Albert Sabin and approved in 1961, contains virus that has been weakened by growing it in monkey kidney cells. This live virus, delivered as oral drops, can replicate in the guts of vaccinated children for several weeks and spread — still weakened — through their faeces to unvaccinated children, allowing immunity to travel through the community. Because it is cheap and easy to administer, OPV has become the polio vaccine of choice, especially in developing countries.

But OPV has a major drawback: the live viruses in the vaccine can mutate, regaining their deadly characteristics. Roughly one

in every 2.7 million children who receive OPV will become paralysed. In those regions where large swaths of the population remain unvaccinated, vaccine-derived polioviruses can regain their ability to circulate and cause outbreaks. "There have been quite a few vaccine-derived poliovirus outbreaks in the past few years," says Nicholas Grassly, who heads the vaccine epidemiology research group at Imperial College London. One recent study[1] estimates that vaccine-derived virus infected 700,000 people between 2005 and 2011, although only a small number of these would have developed paralysis. And these viruses continue to circulate. In 2013, about 60 people were paralysed as a result of circulating vaccine-derived poliovirus, most in a remote region in Pakistan. Eliminating vaccine-derived polio will require an end to the use of OPV. The GPEI advocates not a sudden withdrawal but rather a phased removal of Sabin's vaccine.

All polioviruses fall into one of three groups, or serotypes, and standard OPV contains a weakened version of all three. Types 1 and 3 circulate worldwide, but type 2 wild virus hasn't been seen since 1999 — and viruses derived from the type 2 Sabin strain account for most vaccine-related polio outbreaks. Type 2 is therefore the first to be eliminated from the vaccine. "The continued use of type 2 in the trivalent oral polio vaccine is causing more problems than it is preventing," Miller says.

However, eliminating type 2 from OPV will leave children vulnerable to type 2 vaccine-derived infection. So before making the switch to bivalent OPV — which contains only type 1 and type 3 virus — the plan is to introduce a single dose of IPV, which protects against all three types. Miller says the combination "would protect the population should there be an emergence of a type 2 vaccine-derived strain."

"This is an elegant strategy," says Bruce Aylward, who has led the polio eradication programme at the World Health Organization for the past 15 years.

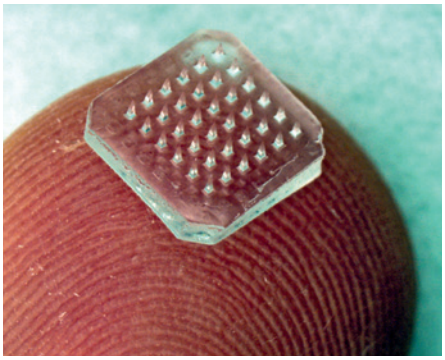
AT THE SHARP END

Elegance does not necessarily translate into ease or economy of implementation, however. OPV typically costs just US$0.14 per dose. But producing IPV requires more virus, and, because it is produced from virulent wild strains, its production demands expensive biosafety measures. It is therefore significantly more expensive. "The best price you can get for IPV is between US$2 and US$3 a dose," says Stephen Cochi, senior adviser at the US Centers for Disease Control and Prevention's Global Immunization Division in Atlanta, Georgia.

The cost of IPV will fall as demand grows — Miller and Aylward hope the poorest countries will be able to secure the vaccine for about US$1 a dose — but it is likely to remain more expensive than OPV. And funds used to purchase IPV won't be available to buy other vaccines for diseases far more common than polio. "A country like Uruguay will have many cases per year of diseases such as pneumonia, meningitis and hepatitis, but may go for 20–30 years without a single vaccine-related case of polio," says Ciro de Quadros, executive vice-president of the Sabin Vaccine Institute in Washington, DC. Such lopsided statistics, he says, will influence investment priorities.

Administering IPV is more problematic, too. Unlike oral drops, injections require trained professionals and sterile syringes. There's also the thorny question of acceptance. In parts of Pakistan and Nigeria, some people are already suspicious of the vaccine. Now health officials must convince parents that their children need not one but two different kinds of polio vaccine.

Researchers are working to help health officials overcome these barriers. Aylward and his colleagues are investigating cost-cutting measures, such as using adjuvants to reduce the amount of virus needed. They have also found



JEONG-WOO LEE

A dissolving microneedle patch on a finger.

that the dose can be reduced if the vaccine is injected under the skin instead of into the muscle[2]. Mark Prausnitz, a chemical engineer at the Georgia Institute of Technology in Atlanta, is working on a version of IPV that could be applied like a band-aid, eliminating the need for syringes and trained medical professionals. The patch contains 100 microneedles, each less than a millimetre long, affixed to a flexible pad smaller than a postage stamp. When the patch is in place, the needles puncture the skin and dissolve in 5–10 minutes, releasing the inactivated virus. Prausnitz recently tested the polio patch in rhesus macaques and found that it raises an immune response just as effectively as the standard injectable vaccine. He and his colleagues are seeking funding to conduct a clinical trial of the patch.

SILENT SPREAD

The challenges posed by IPV extend beyond economics and logistics. IPV is good at protecting against paralysis, but it doesn't evoke a strong immune response in the gut, where polio replicates, so people who are vaccinated with IPV can still spread the virus. Israel made the switch from OPV to IPV in 2005. The country hasn't had a case of paralytic polio since 1988, but authorities continue to monitor the country's sewage for signs of the virus. In the spring of 2013, they found it in the sewers of Rahat in southern Israel. By August the virus had been detected in 91 sewage samples from 27 sites in southern and central Israel, and in faecal samples from 42 people in those regions. "It spread throughout Israel and to the West Bank and Gaza," Cochi says. Because roughly 94% of children in Israel have been vaccinated, not a single child developed the disease. But the continued circulation of the virus puts other countries with lower rates of vaccination at risk.

It is theoretically possible that, once the world begins using bivalent OPV, type 2 vaccine-derived outbreaks could emerge and undergo a similar silent spread because children who had received IPV would probably not develop paralysis[3]. "In Israel they have the most intensive environmental sampling — looking for poliovirus and other pathogens — in the world," Cochi says. But in regions without intensive sampling, the virus could go undetected much longer.

Aylward considers that scenario unlikely, however. He and Grassly recently developed a model to examine the risk and found that, under most conditions, IPV will hasten the virus's demise[3]. But when vaccine coverage is high and the virus has a high reproductive rate, "you could see the situation you see in Israel: persistent circulation," Aylward says. Fortunately, he adds, "not many settings mimic that environment." What's more, the GPEI aims to introduce only a single dose of IPV, so children will have some immunity but won't be fully protected, making it less likely that an outbreak will go undetected. Aylward acknowledges the potential risk of this approach, but he emphasizes the perils of continuing to use an oral vaccine containing all three strains of virus. "The error," he says, "is thinking the current situation is a safe one."

The GPEI's optimistic timeline sees the world certified polio-free in 2018, a result that would allow the complete withdrawal of the oral vaccine. But even if the many obstacles to introducing IPV can be overcome, it may be difficult to introduce it into enough countries in 2015 to prepare for a coordinated withdrawal of type 2 vaccine in 2016. As de Quadros points out, such a rapid rollout would be unprecedented. "The way they are planning the introduction is very ambitious," he says. "It will be interesting to observe what will happen."

That's the problem with endgames. Even with only a few pieces left on the board, it's still not entirely clear how to win the game. ■

Cassandra Willyard *is a freelance science writer based in Madison, Wisconsin.*

1. Burns, C. C. *et al. J. Virol.* **87**, 4907–4922 (2013).
2. Resik, S. *et al. N. Engl. J. Med.* **368**, 416–424 (2013).
3. Mangal, T. D., Aylward, R. B. & Grassly, N. C. *Am. J. Epidemiol.* **178**, 1579–1587 (2013).

PERSPECTIVE


Elimination round

We must push harder to eliminate diseases, for everyone's benefit, say **Andrew Artenstein** and **Gregory Poland**.

Epidemic infectious diseases kill millions each year and cause a massive burden of morbidity in developing countries. These maladies contribute to social upheaval, political turmoil and economic chaos, which threaten country-specific, regional and even global security.

Many of these infections are preventable. Some vaccine-preventable infectious diseases, such as polio, measles and rubella, are subject to aggressive intervention strategies; polio, for example, is targeted for global eradication. So far, only one disease — smallpox — has been globally eradicated. However, sustained vaccination programmes have eliminated several epidemic diseases in developed countries.

The elimination of a disease from a defined geographic region or its worldwide eradication requires sustained global engagement and massive resource investment — a bigger commitment than most developing countries can make and more than the governments of many wealthy nations are willing to provide. Yet the potential rewards are substantial: not just saving lives but keeping people healthy and creating a more stable and secure world.

The regional elimination of polio, part of the campaign to eradicate the disease, illustrates the importance of global engagement and the risks of letting our guard down (see 'The eradication endgame', page 14). According to the World Health Organization (WHO), this ongoing vaccination and surveillance effort, which started in 1988, has involved more than 20 million volunteers working in 125 countries to vaccinate 2.5 billion children at a cost so far of US$9.5 billion. It has reduced the incidence of polio by more than 99% and eliminated endemic transmission in all but three countries[1]. However, the difficulties associated with the campaign are illustrated by the recent outbreak of wild-type polio in China; the virus was imported more than a decade after the country was certified polio-free[2]. Eliminating polio from its last remaining pockets is difficult. It requires ongoing, worldwide vigilance that calls for resources, political will and the focused, sustained commitment of both wealthy and developing nations — because as long as polioviruses circulate anywhere in the world, we all face the threat of disease re-emergence.

A NEW MODEL

Recently, a new campaign has started to eliminate another important, epidemic infectious disease — group A meningococcal meningitis — from the 'meningitis belt' of sub-Saharan Africa. This crippling infection of the central nervous system occurs in devastating, seasonal and cyclic epidemics in sub-Saharan Africa, affecting hundreds of thousands of people, predominantly children and young adults, and killing nearly one in ten infected individuals. Epidemic meningococcal A has been targeted for elimination by the Meningitis Vaccine Project (MVP), a consortium organized through a partnership between the WHO and the non-profit organization PATH, with start-up funding from the Bill & Melinda Gates Foundation[3].

The MVP represents a model for regional disease elimination efforts in two respects. From the outset, its leaders were advised by stakeholder African nations that to achieve the goal of vaccinating more than 300 million people within 15 years, a vaccine would need to be not only safe and effective but also very cheap. Large pharmaceutical companies showed little interest in the sub-Saharan market. Therefore, the MVP established creative alliances with vaccine companies that were outside 'big pharma' and that recognized both the humanitarian benefits and the rewards of positive public exposure[3]. The result was MenAfriVac, a novel, safe, cheap and effective meningococcal conjugate vaccine specifically designed for the at-risk African population[4].

But vaccine development was only the first innovation; the second was MVP's massive, coordinated educational and communication efforts, aimed at engendering extraordinary levels of support among local populations. Between 2010 and 2012, the MVP vaccinated more than 100 million people in 10 African countries. As a result, the number of infections during the 2013 epidemic meningitis season was the lowest in that region for a decade[5].

INTERNATIONAL EFFORTS SUCH AS THE MVP HAVE SHOWN WHAT MIGHT BE ACHIEVED

PUSHING FOR THE FINISH LINE

The MVP has shown that it may be possible to eliminate meningococcal meningitis in sub-Saharan Africa. It has so far taken a monumental effort over 15 years involving thousands of people and hundreds of millions of dollars from the international community and African nations. And even more is required to finish the job: the WHO has estimated that another US$475 million will be needed to deploy MenAfriVac to all meningitis belt countries, and ongoing resources required to sustain disease elimination through surveillance and vaccination.

Epidemic infections that are suitable targets for elimination occur primarily in developing parts of the world where wars, political instability, economic hardship and the lack of infrastructure and trained personnel impede vaccine delivery. The massive investment of people, vaccines, equipment and diagnostics required is daunting but attainable. International efforts such as the MVP have shown what might be achieved. The time is ripe for the developed world to commit to eliminating as many epidemic infectious diseases as possible; the global community will reap the benefits for years to come. ■

Andrew W. Artenstein *is Chair of the Department of Medicine, Baystate Health, Tufts University School of Medicine in Springfield, Massachusetts.* ***Gregory A. Poland*** *is Director of the Mayo Clinic Vaccine Research Group in Rochester, Minnesota.*
Email: artenstein@baystatehealth.org

1. Mundel, T. & Orenstein, W. A. *N. Engl. J. Med.* **369,** 2045–2046 (2013).
2. Luo, H.-M. *et al. N. Engl. J. Med.* **369**, 1981–1990 (2013).
3. LaForce, F. M., Konde, K., Viviani, S. & Prézioso, M.-P. *Vaccine* **25S**, A97–100 (2007).
4. Daugla, D. *et al. Lancet* **383**, 40–47 (2013).
5. WHO. Global Alert and Response (GAR) <http://www.who.int/csr/don/2013_06_06_menin/en/> (2013).

MARMADUKE ST. JOHN/ALAMY

Health-care workers in New York protest against compulsory swine flu vaccination.

PUBLIC HEALTH

An injection of trust

Faced with outbreaks of preventable diseases, public-health experts need to win over parents who refuse vaccinations.

BY MICHAEL EISENSTEIN

In July 2013, public-health officials in Wales finally began to breathe a sigh of relief. The measles epidemic that had raged through the country for eight months and infected more than 1,200 patients — hospitalizing 88 and killing one — was finally coming under control. The respite was brief, however, as just months later a second outbreak emerged in the same region, with 36 new cases by mid-November (see "Exposed and unvaccinated" page S18).

The outbreaks primarily afflicted children whose parents had opted not to let them have the measles–mumps–rubella (MMR) vaccine. Their refusal was broadly attributed to lingering fears related to a now discredited link between the MMR vaccine and autism. Parents remained hesitant even after the first outbreak, and a strong vaccination push reached fewer than half of the eligible children.

The re-emergence of vaccine-preventable diseases has become increasingly common worldwide. For example, in 2012 the US Centers for Disease Control and Prevention (CDC) in Atlanta, Georgia, reported the largest number of US cases of pertussis (whooping cough) for nearly 60 years. In Japan, rubella cases leapt from 87 in 2010 to 5,442 in just the first 4 months of 2013. And in France, the World Health Organization (WHO) reported 14,000 cases of measles in 2011. "There are lots of examples in wealthy, developed countries," says Seth Berkley, chief executive of the Global Alliance for Vaccination and Immunization (GAVI) in Geneva, Switzerland. Given the narrow margins of ensuring protection against such outbreaks, even a few parents who refuse paediatric vaccination can jeopardize the control and elimination of diseases that are prominent killers of infants and children elsewhere in the world.

➲ NATURE.COM
For some of the latest research on immunization:
nature.com/nm

Vaccine refusal dates back to the nineteenth century, when the UK Government permitted 'conscientious exemption' for those opposed to smallpox vaccination. But today's reasons for refusal are very different. "We ask citizens to get vaccines to prevent 14 different diseases, which can mean as many as 26 inoculations in the first few years of life, to prevent diseases that people mostly don't see, using biological fluids that most people don't understand," says Paul Offit, head of the infectious-diseases division at the Children's Hospital of Philadelphia in Pennsylvania. "It's not surprising that people are hesitant."

PERSONAL REASONS

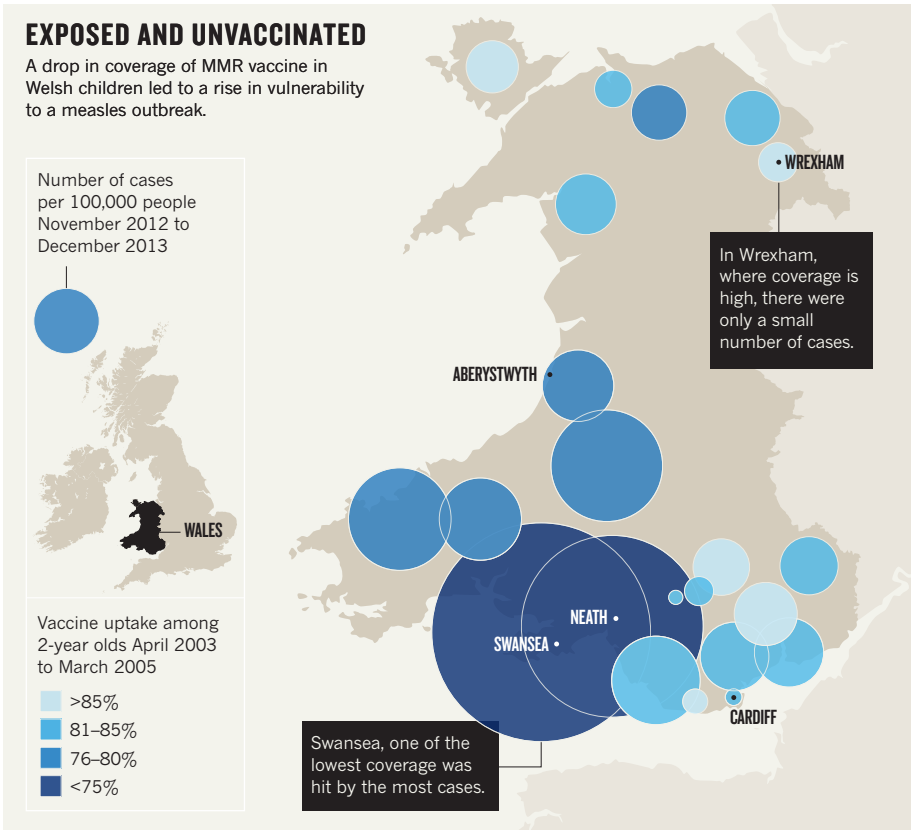
Most public-health experts view vaccination programmes as unalloyed successes. One analysis estimates that immunization has prevented 75–106 million cases of disease in the United States alone[1]. Since the 1980s, every US state has required a standard battery of vaccines for school enrolment. There is strong participation too in much of Western Europe, where these vaccines are merely 'recommended'. "The vast majority of children are immunized, with coverage of over 90% across Europe," says Pier Luigi Lopalco, head of the vaccine-preventable diseases programme at the European Centre for Disease Prevention and Control (ECDC) in Stockholm. When Australia faced falling vaccination rates in the 1990s it introduced incentives that rewarded both clinics and parents. "Our immunization rates rose by at least 10%, which was a major increase," says Julie Leask, a social scientist specializing in immunization policy at the University of Sydney.

But some vaccination programmes allow people to refuse for personal reasons. In much of Europe, no medical consultation is required. In the United States, parents must actively register their refusal; 48 states recognize religious exemptions and 18 allow 'personal belief exemptions'. The refusal numbers are low — just 2% for 2010–2011, according to the CDC — but epidemiologist Saad Omer of Emory University in Atlanta, Georgia, has observed a disconcerting rise. "The rate of refusal has gone up, and even the rate of change compared to previous years has accelerated," he says. Indeed, CDC data indicate that the percentage of non-medical exemptions essentially doubled between 2006 and 2011. Different states require different levels of effort: some require medical consultation, others simply a signature. Omer found that non-medical exemption rates were 2.3 times higher in states with easy requirements than in those with steeper administrative barriers[2]. "If you make it easier for a parent who is hesitant and on the fence to claim an exemption, it looks like they will," he says.

Unvaccinated families also tend to cluster. Leask notes that in Australia "the refusal rate is 1.7% nationally, but in some regions that can climb to around 20%." Some clustering also occurs in self-contained religious groups. The 'Bible Belt' region of the Netherlands, which is home to several communities of Orthodox Protestants that have rejected vaccination, has been the site of a large ongoing measles outbreak, and in October 2013 an unvaccinated 17-year-old girl died from measles. More recently, international travellers have enabled this epidemic to make the leap to Canada.

SCARE STORIES

Instead of religious dogma, many clusters of vaccine refusals result from shared concerns about whether children may be harmed by the inoculations. "Refusal is multifaceted, but perceptions of vaccine safety contribute more than other factors," says Omer. These worries can result in delayed vaccination, outright refusal or selective inoculation of children, where the



PUBLIC HEALTH WALES

decision is a product of both risk calculation and emotional response.

A single scare can cast a long shadow. The story of Andrew Wakefield, a gastroenterologist at the Royal Free Hospital in London whose work led to a widespread belief in a link between the MMR vaccination and autism, is well known. As parents panicked, MMR vaccination rates in England and Wales fell from over 90% in 1997 to less than 80% in 2004, with similar drops in the United States and across Western Europe. Although thoroughly discredited, Wakefield's ideas are kept in circulation by vocal networks of anti-vaccine activists. "In southern Europe, especially Italy, this alleged link between autism and MMR is re-emerging in the newspapers and on a lot of websites," says Lopalco. Activist organizations also promote unfounded fears that vaccines trigger medical conditions such as multiple sclerosis or contain toxic levels of chemicals such as aluminium, or that infants' immune systems are overwhelmed by the number of vaccinations[3].

In fact, vaccines undergo extensive and continuous surveillance to identify adverse events overlooked during clinical trials. For example, the CDC operates the Vaccine Safety Datalink (VSD) with nine large US 'managed care organizations', tracking data from more than 9 million individuals. "We can update these databases weekly, and thus virtually conduct real-time monitoring when a new vaccine is introduced," says Frank DeStefano, director of the CDC's Immunization Safety Office. Data from the VSD helped disprove the connection between MMR and autism, but have also identified real adverse events, such as when 197 children in a cohort of 1.8 million who had received the MMR vaccination developed immune thrombocytopaenic purpura[4]. "It's a relatively benign blood disorder where there's easy bruising and bleeding, but it can be scary," says Jason Glanz, an epidemiologist affiliated with the VSD at the Kaiser Permanente Institute for Health Research in Denver, Colorado.

The CDC continues to fight the myth of a vaccine–autism link and recently demonstrated that there was no link between exposure to numerous vaccine antigens and autism[5]. "A substantial proportion of parents still have concerns along these lines," says DeStefano. Leask notes that the MMR story draws strength from the lack of a robust biological explanation for autism. "This causal hunger drives people to look around for a culprit," she says, adding that vaccines were once linked to sudden infant death syndrome (SIDS) until the medical community got a better understanding of the risk factors.

FORGOTTEN FOES

Studies suggest that parents who delay or refuse vaccines tend to be well educated and seek out information that gives them active control of their child's health. Some consult practitioners of complementary and alternative medicine, who may eschew vaccines in favour of non-pharmaceutical approaches to preventing diseases, or promote alternative vaccine schedules that leave children underprotected. Based on a large study of undervaccination in eight managed care organizations, Glanz concluded that at least 12–13% of parents "are deliberately not giving vaccines on time."

Many parents also visit anti-vaccination websites that use anecdotal evidence to promote an agenda of parental choice that builds on an underlying mistrust of the government and the pharmaceutical industry[3]. "They use narratives and tell stories," says Neal Halsey, director of the Institute for Vaccine Safety at the Johns Hopkins Bloomberg School of Public Health in Baltimore, Maryland. "We present numbers and risk levels, and those things don't resonate with hesitant parents."

For such parents, emotional descriptions of children who have allegedly been injured by vaccines may prove more persuasive than tales of half-forgotten diseases. "My wife ran the intensive care unit at a major teaching hospital in America, and she's never seen a case of measles or tetanus," says Berkley. "I think that's a big factor." He points out that vaccines are generally embraced in the developing world, where these diseases remain all too real — the WHO estimates that 158,000 people died from measles in 2011. "In general, people there desperately want vaccines and will walk for a day to get them," he says. But in nations with long-standing vaccination programmes, such as the United States or United Kingdom, it's easy to dismiss these diseases as harmless unless you've experienced the potential complications, which include pneumonia and encephalitis. "When I've talked with parents of unvaccinated children who have been admitted to hospital with complications from pertussis or measles, they inevitably say, 'I never knew it could be this serious'," says Halsey.

If large numbers of parents continue to opt out of vaccination programmes, these may well become more familiar experiences. In a well-vaccinated community, even unvaccinated individuals benefit from herd immunity. The threshold for this benefit depends on both the disease and the vaccine; for measles, the CDC estimates that herd immunity requires 92–94% vaccine coverage. But herd immunity breaks down when coverage drops even in small pockets of otherwise well-vaccinated regions. Omer and colleagues found that this effect may have contributed to a 2010 pertussis outbreak in California that infected more than 9,000 individuals[6]. "The clustering of refusals was associated with the clustering of pertussis," says Omer. Pertussis is particularly problematic because the vaccine is less protective than others and its effectiveness wanes over time. Loss of herd immunity could also help more serious diseases to return: the detection of poliovirus in Israel and outbreaks in war-torn Syria led the ECDC to announce[7] that such countries "should urgently consider implementing targeted action and improving vaccine coverage".

Wary parents are only part of the problem. "It's also people who haven't gotten up to date, either unwittingly or because they have fallen through the cracks," says Leask. But those who sit on the fence represent a potentially serious gap in a nation's immunity, and the MMR panic has shown how quickly this gap can widen.

OFF THE FENCE

The trick is to address worries while preserving public confidence — often a difficult balancing act. Controversy lingers over a 1999 recommendation from the CDC and the American Academy of Pediatrics to remove the ethyl mercury-containing preservative thiomersal from single-dose vaccines. This precaution was based on concerns over cumulative environmental mercury exposure in children, although subsequent research showed that ethyl mercury is eliminated from the body much faster than predicted. Offit believes this decision fuelled misconceptions that thiomersal contributes to autism. "We branded it with a scarlet letter, and today people are still scared of getting flu vaccines in the multidose preparations that contain thiomersal," he says. However, Halsey defends the decision as necessary to protect public trust. "None of us had any concerns about autism," he says. "But if we had not done it, I think that more people would be rejecting those vaccines." In other cases, the negative impact is clearer. For example, France still has poor uptake of the hepatitis B vaccine following the government's 1998 suspension of vaccination, a decision based on false reports of a link with multiple sclerosis.

When the press spotlights potential adverse events, especially with backing from celebrities such as actress Jenny McCarthy or high-profile scientists such as Wakefield, it can even shake the faith of medical professionals. "If you have a provider who is less confident in a vaccine's safety and less motivated, that will have a lot of carry-over effects," says Leask.

Heidi Larson of the London School of Hygiene and Tropical Medicine helps public-health experts respond rapidly to avoid creating a lingering atmosphere of doubt by identifying pockets of concern early (see "Adverse reactions"). "Publics have long memories," says Larson. "We need to be vigilant and never for a minute take for granted any individual's acceptance of any health technology." Larson directs the Vaccine Confidence Project (VCP), which scans news and social media for signs of concern[8]. "We're trying to use a systematic approach to characterize what breeds confidence and lack of confidence, and identify things that tip it one way or another," she says. Networks of pro-immunization parents are also helping to counter anti-vaccine propaganda. For example, epidemiologist Edgar Marcuse of the University of Washington in Seattle is recruiting such parents as peer-educators through the Vax Northwest programme to lower his state's exemption rate.The final decision on whether to vaccinate, however, happens in the clinic. "Even among vaccine refusers, we found that primary health-care providers were the most frequently used and trusted source of vaccine information," says Omer. Honesty is the best policy. Like any medicine, vaccines carry real risks, ranging from minor swelling to rare but serious events such as seizures or anaphylaxis, and doctors can build trust by candidly framing these facts alongside the dangers of disease.

"If you put boundaries around the risk and you say what it is, it becomes much less mysterious," says Leask. Her team has devised a decision-support framework that helps clinicians to deliver targeted information for parents who are cautious supporters, hesitant or ardent refusers. The emphasis is on winning over the parents through listening and empathy, rather than challenging contrary beliefs. Ideally, she says, this intervention will be delivered before the baby is, reaching mothers ahead of any decisions about vaccination.

Offit notes that in his experience, the trump card of medical authority also helps. "Both parents and doctors want to do what's best for the child," he says. "But they're coming for your expertise — it's okay to be an expert." ■

Michael Eisenstein *is a freelance journalist based in Philadelphia, Pennsylvania*

CASE STUDY

Adverse reactions

Vaccination initiatives are generally welcomed in the developing world, where disease mortality and morbidity remain clearly visible threats, but even there they are vulnerable to misinformation and miscommunication. In the mid-1990s, a Catholic organization disseminated misinformation that the tetanus vaccine had contraceptive effects. Vaccination rates plummeted in Catholic communities until public-health professionals reached out to the Vatican to help resolve the crisis.

The handling of such conflicts can make or break a vaccination programme. In 2003, northern Nigeria boycotted the polio vaccine, fuelled by political issues and mistrust of the Western pharmaceutical industry and by rumours that the vaccine was a plot to sterilize Muslims. The public-health community overcame this boycott (and a similar movement in India) by working with local Islamic clergy and community leaders. In contrast, two demonstration projects for the human papillomavirus vaccine in India were derailed in 2010 by campaigners from women's groups. After early attempts to engage the national government over the programme were rebuffed, the activists mounted an aggressive campaign calling for an investigation of the deaths of four vaccine recipients. The deaths proved unrelated to the vaccine, but the projects were halted amid public opposition. "[The protesters] started talking about things related to it being too expensive, not giving cervical screening, and the need to have a public forum," says Heidi Larson of the London School of Hygiene and Tropical Medicine. "They didn't initially focus on the vaccine safety issue, but when they weren't being listened to, they searched for adverse events because that gets more of a reaction."

Larson believes that more attentive monitoring of online expressions of public concern — through her Vaccine Confidence Project (VCP), for example — could bring attention to these issues sooner. Local protests are often fuelled by online activists in the United States and Europe. By keeping tabs on rumours and reports of possible adverse events, governments and public-health officials can adapt engagement strategies accordingly. This won't solve every problem — Larson notes that recent attacks against vaccination workers in Pakistan and Nigeria are the acts of militants, rather than expressions of public refusal. More generally, however, the VCP could help to engage disenfranchised communities early, before boycotts or protests become necessary. "We're trying," says Larson, "to be anticipatory, rather than in crisis management." ***M. E.***

REUTERS/GEORGE ESIRI

Polio vaccination in Nigeria.

1. van Panhuis, W. G. *et al. N. Engl. J. Med.* **369,** 2152–2158 (2013).
2. Omer, S. B. *et al. N. Engl. J. Med.* **367,** 1170–1171 (2012).
3. Kata, A. *Vaccine* **30**, 3778–3789 (2012).
4. O'Leary, S. T. *et al. Pediatrics* **129**, 248–255 (2012).
5. DeStefano, F. *et al. J. Pediatr.* **163**, 561–567 (2013).
6. Atwell, J. E. *et al. Pediatrics* **132**, 624–630 (2013).
7. *Risk Assessment: Wild-type Poliovirus 1 Transmission in Israel — What is the Risk to the EU/EEA?* (European Centre for Disease Prevention and Control, 2013).
8. Larson, H. J. *et al. Lancet Infect. Dis.* **13**, 606–613 (2013).

PERSPECTIVE

Ill prepared for a pandemic

Klaus Stöhr asks whether those responsible for public health will grasp new opportunities to ensure pandemic vaccine readiness.

Over the last 500 years, there have been, on average, three severe influenza pandemics in each century. The most recent pandemic was declared in 2009. Yet despite much investment in public health and many improvements in vaccine production techniques and know-how, the availability of influenza vaccines during this event was far from adequate. Six months into the pandemic, 534 million doses were available, and after one year that number had risen to 1.3 billion — enough for only 8% and 25%, respectively, of the world population. We were lucky that the pandemic declared in 2009 turned out later to be mild and that just one shot of vaccine was sufficient to protect most people. This is not usually the case during a severe influenza pandemic.

Unless there are fundamental changes in both influenza vaccine manufacturing and global pandemic preparedness, another pandemic will mean that vaccines will again be in very short supply and available in only a few, developed countries.

LIMITS IN PRODUCTION

Only a few factors currently limit the timely supply of pandemic vaccines, but unfortunately these factors are fundamental. One is that seasonal and pandemic influenza vaccines are produced by similar technologies in the same facilities, using methods that rely almost exclusively on embryonated chicken eggs. The existing level of production in these seasonal-vaccine facilities can rapidly increase only marginally, and it would take years to bring new facilities online, which means that production cannot be expanded quickly enough to keep pace with the spread of a pandemic virus that will go global within days or weeks of detection.

Even when production is switched to pandemic vaccines, it will take 3 or 4 months for the first doses to become available — by which time outbreaks might have already peaked on some continents. A large part of this delay is the time required to isolate and characterize the virus, prepare the vaccine prototype and adapt the manufacturing process, and prepare reagents for vaccine release.

The production capacity for seasonal influenza vaccines is closely matched to annual demand; it is not sustainable to keep excess manufacturing capacity idle. Over the past ten years, the annual output of seasonal vaccine has doubled to approximately 450 million doses[1], which can be ramped up in the event of a pandemic to give a total potential capacity of around 850 million doses. However, as was shown during the 2009 pandemic, that is not even close to providing the billions of doses that would be required in the short time available.

On the positive side, there have recently been some promising developments in influenza vaccine research that could address several of these shortcomings. None, however, is yet in later-stage clinical development.

Should we face another pandemic in the next few years, the scope of the vaccine response would probably be similar to that of 2009. There is one major difference, however: over the last few years, a considerable portion of global pandemic production capacity has been pre-booked by some countries. This ensures that they will have access to the precious vaccine doses supplied during the crucial first 6–8 months of a pandemic.

FIVE-YEAR OUTLOOK

As countries continue to pre-book pandemic supply, it is more and more likely that the limited vaccines available during the first months of any pandemic during the next few years will be sold out almost completely. Some companies might hold capacity to address any manufacturing and vaccine formulation uncertainties. Some might decide to allocate up to 10% of their pandemic vaccine output to the World Health Organization (WHO), as required in its Pandemic Preparedness Framework Agreement, in exchange for receiving pandemic strains to be used for vaccine production. But these doses will vanish into the large supply gap that will face developing countries.

NATIONAL AND GLOBAL HEALTH AUTHORITIES NEED TO CHANGE COURSE AND EMBRACE THESE DEVELOPMENTS

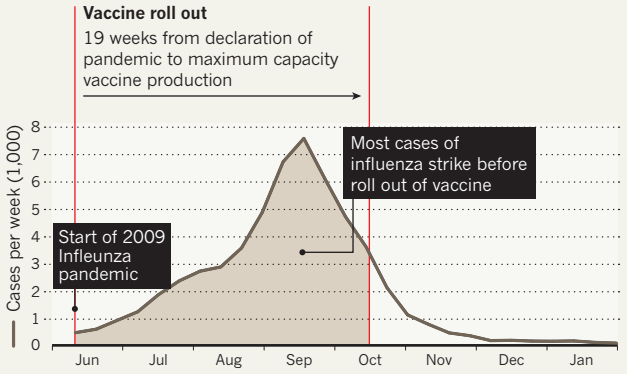
On the production side, there are no radical changes on the horizon for the next few years. True, some recently introduced vaccines are produced using cell culture and recombinant technology. But most production sites still use eggs — and so, in the near future, the impact of these newer production methods on global supply will probably be limited. The speed with which manufacturers can ramp-up or expand influenza production to meet pandemic demand will not fundamentally change in the next few years.

Vaccine production capacity is driven by demand: the increase in capacity mentioned earlier resulted mainly from improvements in vaccine coverage in developed countries. To put things into perspective, more than three-quarters of the annual seasonal influenza vaccine doses that are produced globally are consumed by just 12 countries in North America and Europe[2], and most of the rest go to Japan and Australia. Coverage in these countries is showing signs of plateauing. In developing countries, by contrast, the demand for seasonal influenza vaccine is likely to remain negligible in the coming years. In these countries, most immunization efforts will continue to focus on diseases covered by the WHO's Extended Programme on Immunization, together with other diseases such as those caused by rotavirus, pneumococcus and human papillomavirus. With the help of organizations such as the WHO, a few pilot vaccine production plants might go online in Asia, but without sustainable seasonal vaccine demand, large-scale influenza manufacturing in developing countries will remain untenable.

For these reasons, it is highly unlikely that global seasonal

LATE TO THE PANDEMIC

Influenza vaccine doses became available in large quantity only after the 2009 pandemic had peaked. Data shown are from a northern hemisphere country that had in place a significant pandemic preparedness program.



influenza vaccine capacity will increase to the projected 1.75 billion doses in 2015 that was forecast in the WHO's Pandemic Influenza Preparedness Framework. It is much more likely that the maximum annual capacity will remain at around 400 million doses above the seasonal demand of 550 million doses in 2014. As a consequence, instead of capacity increasing, this could lead to current expansion plans not materializing or existing production capacity being shut down in response to market dynamics, including the current rapid price erosion of seasonal influenza vaccines.

One way to stretch the limited seasonal production capacity during a pandemic is to add a proven, safe, antigen-sparing adjuvant, which could multiply vaccine output by as much as 12 times. A safe adjuvant will also be required to increase the duration of protection against the influenza variants that are likely to arise from an initial pandemic virus. Manufacturers of influenza vaccines will probably seek to license the rights to produce an adjuvant that has been developed by another firm, purchase and stockpile a suitable adjuvant or — in what would be a costly and long-term undertaking — develop their own.

Other developments are at hand to improve the speed of vaccine production. Using synthetic biology[3], it is possible to shorten the time needed to prepare the crucial vaccine candidate seeds from 4–6 weeks using conventional methods to less than 1 week. In 2013, candidate vaccine strains for the H7N9 outbreak were swiftly prepared using such new technologies for the first time[4]. New tests have been developed that expedite the release of vaccine batches, shaving a month off the time needed for vaccine formulation and delivery. These tests are being introduced into the regulatory frameworks so that they can replace the slower existing tests. Together, these advances could mean that the first vaccine doses are ready for use 1–2 months earlier than is possible using conventional methods.

LONG-TERM CHANGES

Even with a modest increase in production capacity and a small but appreciable reduction in the time taken to deliver the first doses of a vaccine, most of the world's population — especially those outside the developed world — will be as vulnerable as ever to another pandemic in the coming years.

The best hope for a change in the status quo comes from the introduction of revolutionary influenza vaccine production technologies. Ideally, it would be sustainable to run such technologies below capacity, with the possibility of quickly ramping up output in the face of a pandemic. Such technologies, if they also offered economies of scale, could help to prompt the sustainable introduction of seasonal influenza vaccines into developing countries, which would in turn increase demand for the vaccines and thus manufacturing capacity. However, at present the global public health research community seems to be paying little or no attention to this possibility.

The new technologies that seem to have the greatest potential include self-amplifying RNA vaccines and, to a lesser extent, plant-derived vaccines and haemagglutinin-based bacterial expression systems. There are several companies investing in RNA vaccines; if this platform and the RNA vaccines prove to be stable, and the encouraging results from preclinical tests are confirmed in humans, this technique could be used to provide almost immediate pandemic vaccine responses. Fill-finishing capacity would need to be externally contracted in advance.

Another potential solution to pandemic readiness would be the development of a universal influenza vaccine that could be either used for pre-pandemic priming or produced at sufficient speed and quantity for use during a pandemic. Either approach would represent a breakthrough in pandemic preparedness; research towards these goals will improve the seasonal vaccine in the interim. But the goal of covering all subtypes of influenza-A with one vaccine, produced in a way that can be ramped up quickly during a pandemic, seems decades away at best.

If the capacity to produce pandemic vaccines quickly is to be increased, it will be important to raise the demand for seasonal influenza doses around the world, including in developing countries. Seasonal influenza has significant health impacts in all climate zones; with sustained economic growth, more countries will be able to afford the vaccines. Such an increase in demand, if sustainable, will lead to the creation of more production capacity in developing countries, and thus to an increase in global capacity.

A NEW APPROACH

The limitations of the existing influenza vaccine production technologies are the fundamental reasons for the seemingly insurmountable gap in pandemic vaccine supply. Addressing these limitations could help to bring about an affordable and equitable pandemic vaccine supply and also pave the way for the introduction of seasonal influenza vaccines in developing countries. Some of the recently developed vaccine production technologies have the potential to resolve the pandemic vaccine dilemma; they could even have broader applications for the prevention of other communicable diseases. Unfortunately, global public-health authorities have so far failed to make the strategic investments needed to effect these changes in the influenza vaccine landscape. The visible trend seems to be that of maintaining current practice, despite the evidence of its inadequacy during the 2009 pandemic.

National and global health authorities need to change course and embrace these developments. In so doing, they can create a new era of pandemic preparedness. ■

Klaus Stöhr *is vice president and global head of policy at Novartis Vaccines and Diagnostics, Cambridge, Massachusetts, and former head of the WHO Global Influenza Program.*
Email: klaus.stohr@novartis.com

1. Collin, N. & de Radiguès, X. *Vaccine* **27**, 5184–5186 (2009).
2. Palache, A. *Vaccine* **29**, 9459–9466 (2011).
3. Dormitzer, P. R. *et al. Sci. Transl. Med.* **5**, 185ra68 (2013).
4. Settembre, E. C. *Hum. Vaccin. Immunother.* doi: 10.4161/hv.27600 (2013).